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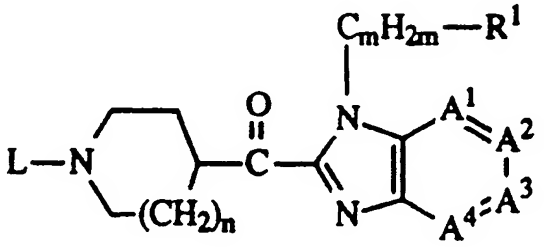
(54) Title: NOVEL 4-PIPERIDINYLCARBONYL DERIVATIVES



(I)

(57) Abstract

4-piperidinylcarbonyl derivatives having formula (I), wherein -A^1=A^2-A^3=A^4- is a bivalent radical having the formula -CH=CH-CH=CH- (a-1), -N=CH-CH=CH- (a-2), -CH=N-CH=CH- (a-3), -CH=CH-N=CH- (a-4), -CH=CH-CH=N- (a-5), -N=CH-N=CH- (a-6) or -CH=N-CH=N- (a-7); R^1 is aryl[1] or a radical of formula -D-R^2 wherein D is O or S; R^2 is C_{1-6}alkyl optionally substituted with hydroxy, C_{1-6}alkyloxy, carboxyl or C_{1-6}alkyloxy-carbonyl; m is 1, 2, 3 or 4; n is 0, 1 or 2; L is hydrogen; C_{1-12}alkyl; C_{3-6}cycloalkyl; C_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; -Alk-R^3 (b-1); -Alk-Y-R^4 (b-2); -Alk-Z^1-C(=X)-Z^2-R^5 (b-3); -CH_2-CHOH-CH_2-O-R^6 (b-4) or -Alk-CHOH-R^{14} (b-5); wherein Alk is C_{1-6}alkanediyl; R^3 is cyano, aryl or Het; R^4 and R^5 are hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het; R^6 is aryl or naphthalenyl; R^{14} is aryl; Y is O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl; Z^1 and Z^2 independently are O, S, NR^8 or a direct bond; R^8 being hydrogen or C_{1-6}alkyl; X is O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano; provided that when -A^1=A^2-A^3=A^4- is a radical of formula (a-1) and R^1 is phenyl optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxy, halo or hydroxy; then L is other than hydrogen, C_{1-6}alkyloxycarbonyl or other than a radical of formula -Alk-R^3 (b-1), -Alk-O-R^4 (b-2-a), -Alk-C(=O)-R^5 (b-3-a) or -Alk-CHOH-R^{14} (b-5) wherein R^3, R^4, R^5 and R^{14} are phenyl optionally substituted with halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof having antihistaminic properties, compositions containing the same and methods of treating warm-blooded animals suffering from allergic diseases.

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+ DESIGNATIONS OF "SU"

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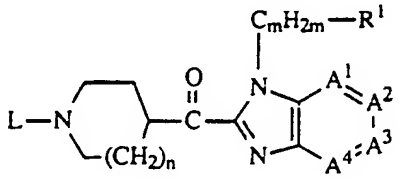
NOVEL 4-PIPERIDINYLCARBONYL DERIVATIVES

Background of the invention

In EP-A-0,363,963 there are described some carbonyl and hydroxymethylene-benzimidazoles useful as antihistaminics. In EP-A-0,411,631 there are described some further carbonyl and hydroxymethylene benzimidazole derivatives as anti-psychotic compounds. In US-4,695,575; EP-A-0,206,415; EP-A-0,282,133; EP-A-0,297,661 and EP-A-0,378,254 there are disclosed methylenebenzimidazole and methyleneimidazopyridine derivatives useful as antihistaminics and serotonin antagonists.

Description of the invention

The present invention is concerned with novel carbonyl derivatives having the formula :



(I),

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

-CH=CH-CH=CH-	(a-1),
-N=CH-CH=CH-	(a-2),
-CH=N-CH=CH-	(a-3),
-CH=CH-N=CH-	(a-4),
-CH=CH-CH=N-	(a-5),
-N=CH-N=CH-	(a-6) or
-CH=N-CH=N-	(a-7);

wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy or trifluoromethyl;

R^1 is aryl[1] or a radical of formula -D-R^2 wherein D is O or S; R^2 is C_{1-6}alkyl optionally substituted with hydroxy, C_{1-6}alkyloxy, carboxyl or C_{1-6}alkyloxycarbonyl;

m is 1, 2, 3 or 4;

n is 0, 1 or 2 ;

L is hydrogen; C_{1-12}alkyl; C_{3-6}cycloalkyl; C_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; or a radical of formula :

-Alk-R^3	(b-1);
-Alk-Y-R^4	(b-2);
-Alk-Z^1-C(=X)-Z^2-R^5	(b-3);
-CH_2-CHOH-CH_2-O-R^6	(b-4); or
-Alk-CHOH-R^{14}	(b-5); wherein

Alk is C_{1-6}alkanediyl;

R^3 is cyano, aryl or Het;

R^4 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^5 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^6 is aryl or naphthalenyl;

R^{14} is aryl;

Y is O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl ;

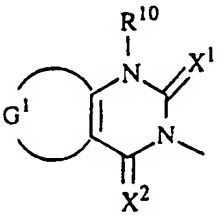
Z^1 and Z^2 each independently are O, S, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl;

X is O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano;

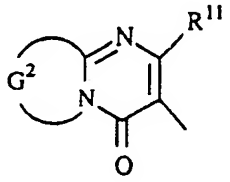
each Het is selected from pyridinyl optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di(C_{1-6}alkyl)-amino, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy and hydroxy; pyrimidinyl optionally substituted with one or two substituents each independently selected from halo, amino, C_{1-6}alkylamino, C_{1-6}alkyl and C_{1-6}alkyloxy; pyridazinyl optionally substituted with C_{1-6}alkyl or halo; pyrazinyl optionally substituted with halo, amino or C_{1-6}alkyl; thienyl optionally substituted with halo or C_{1-6}alkyl; furanyl optionally substituted with halo or C_{1-6}alkyl; pyrrolyl optionally substituted with C_{1-6}alkyl; thiazolyl optionally substituted

with C_{1-6}alkyl; imidazolyl optionally substituted with one or two substituents each independently selected from C_{1-6}alkyl, arylC_{1-6}alkyl and nitro; 1,3,4-thiadiazolyl optionally substituted with C_{1-6}alkyl or amino; oxazolyl optionally substituted with C_{1-6}alkyl; 2,3-dihydro-1,4-benzodioxinyl optionally substituted with C_{1-6}alkyl or halo; 2-oxo-2H-1-benzopyranyl and 4-oxo-4H-1-benzopyranyl both being optionally substituted with C_{1-6}alkyl; 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl optionally substituted with C_{1-6}alkyl; 6-purinyl; and

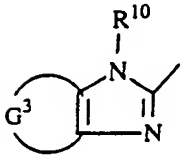
a bicyclic heterocyclic radical of formula



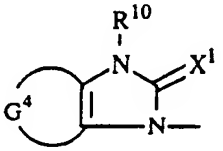
(c-1),



(c-2),



(c-3),



(c-4),

wherein

X^1 and X^2 each independently are O or S ;

each R^{10} is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl;

R^{11} is hydrogen, C_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, halo or C_{1-6}alkyloxycarbonylC_{1-6}alkyl ;

G^1 is -CH=CH-CH=CH-; -S-CH=CH- or -N=CH-NH- ;

G^2 is -CH=CH-CH=CH-, $-(CH_2)_4$-, $-S-(CH_2)_2$-, $-S-(CH_2)_3$-, -S-CH=CH-, -CH=CH-O-, $-NH-(CH_2)_2$-, $-NH-(CH_2)_3$-, -NH-CH=CH-, -NH-CH=N-, -NH-N=CH- or -NH-N=CH-CH_2-;

G^3 is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

G^4 is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

wherein one or two hydrogen atoms in said radicals G^1, G^2, G^3 or G^4 may be replaced by C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxy or halo, when connected to a carbon atom; or by C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl or arylC_{1-6}alkyl when connected to a nitrogen atom;

each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl;

each $aryl^1$ is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl; thienyl; halothienyl; furanyl optionally substituted with C_{1-6}alkyl and/or hydroxyC_{1-6}alkyl; pyridinyl optionally substituted with C_{1-6}alkyl; pyrimidinyl; pyrazinyl; thiazolyl optionally substituted with C_{1-6}alkyl; imidazolyl optionally substituted with C_{1-6}alkyl; or oxazolyl optionally substituted with one or two C_{1-6}alkyl or hydroxyC_{1-6}alkyl radicals;

provided that when $-A^1=A^2-A^3=A^4-$ is a radical of formula (a-1) and R^1 is phenyl optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxy, halo or hydroxy; then L is other than hydrogen, C_{1-6}alkyloxycarbonyl or other than a radical of formula -Alk-R^3 (b-1), -Alk-O-R^4 (b-2-a), -Alk-C(=O)-R^5 (b-3-a) or -Alk-CHOH-R^{14} (b-5) wherein R^3, R^4, R^5 and R^{14} are phenyl optionally substituted with halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy.

The compounds of formula (I) wherein Het is substituted with hydroxy, mercapto or amino, may also exist in their tautomeric forms. Such forms although not explicitly indicated hereinabove, are intended to be included within the scope of the invention.

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-6}alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl, pentyl and the like; C_{1-12}alkyl defines C_{1-6}alkyl radicals as defined hereinabove and the higher homologs thereof having from 7 to 12 carbon atoms; C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C_{3-6}alkenyl defines straight and branch chained hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; and the carbon atom of said C_{3-6}alkenyl being connected

to a nitrogen atom preferably is saturated; C_{1-6}alkanediyl defines bivalent straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butane-diyl, 1,5-pentane-diyl, 1,6-hexanediyl and the branched isomers thereof.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. Said salt forms can conveniently be obtained by treating the base form of the compounds of formula (I) with appropriate acids such as inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The term acid addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The compounds of this invention may have several asymmetric carbon atoms in their structure. As usual, each of these chiral centers may be indicated by the stereochemical descriptors R and S. The stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

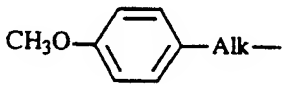
Aryl as used in the definition of R^3, R^4, R^5 and R^{14}, in particular is phenyl optionally substituted with halo, C_{1-6}alkyl, hydroxy or C_{1-6}alkyloxy; aryl as used in the definition of R^6 in particular is phenyl optionally substituted with halo.

Preferred compounds comprise those compounds of formula (I) wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical of formula (a-1), (a-2) or (a-5); R^1 is phenyl optionally substituted with halo, furanyl optionally substituted with C_{1-6}alkyl, or oxazolyl optionally substituted with C_{1-6}alkyl; m is 1 or 2; n is 1; L is hydrogen, C_{1-12}alkyl, C_{1-6}alkyloxycarbonyl, or a radical of formula (b-1), (b-2) or (b-3), wherein R^3 is cyano, aryl or Het; R^4 is hydrogen or Het; R^5 is C_{1-6}alkyl; Y is O or NH; Z^1 and

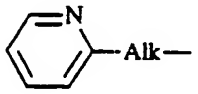
Z^2 each independently are NH or a direct bond; X is O; each Het is selected from pyridinyl, pyrimidinyl, thiazolyl, 2,3-dihydro-1,4-benzo-dioxinyl, 2-oxo-2H-1-benzopyranyl, 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl, or a bicyclic heterocyclic radical of formula (c-1), (c-2), (c-3) or (c-4), wherein X^1 and X^2 each independently are O or S ; each R^{10} is hydrogen, C_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; each R^{11} is C_{1-6}alkyl; G^1 is -CH=CH-CH=CH-; G^2 is -CH=CH-CH=CH-, $-(CH_2)_4-$, $-S-(CH_2)_2-$, $-S-(CH_2)_3-$, -S-CH=CH-; G^3 is -N=CH-CH=CH-; G^4 is -CH=CH-CH=CH-; aryl is phenyl optionally substituted with C_{1-6}alkyloxy.

More preferred compounds are those preferred compounds wherein m is 1, L is C_{1-4}alkyl or a radical of formula (b-1) or (b-2), wherein R^3 is aryl or Het; R^4 is Het; Y is NH; each Het is selected from pyridinyl, pyrimidinyl, or a bicyclic heterocyclic radical of formula (c-2), wherein R^{11} is C_{1-6}alkyl; G^2 is -CH=CH-CH=CH-, $-S-(CH_2)_2-$, $-S-(CH_2)_3-$, -S-CH=CH-; aryl is phenyl optionally substituted with C_{1-6}alkyloxy.

Most preferred compounds are those more preferred compounds wherein R^1 is halophenyl, furanyl optionally substituted with methyl, or oxazolyl optionally substituted with methyl; L is methyl or a radical of formula :



(d-1) ;



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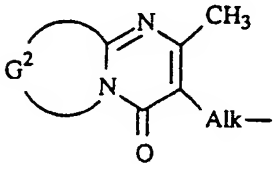
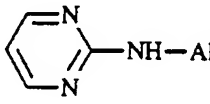
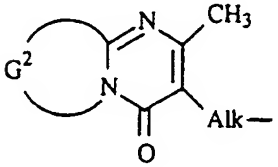


(d-3) ; or

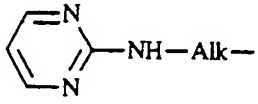


(d-4).

Interesting compounds are those compounds of formula (I) wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula -CH=CH-CH=CH- (a-1), -N=CH-CH=CH- (a-2), or -CH=CH-CH=N- (a-5); R^1 is 4-fluorophenyl or oxazolyl optionally substituted with methyl; m is 1; n is 1 ; and L is a radical of formula



(d-3) or

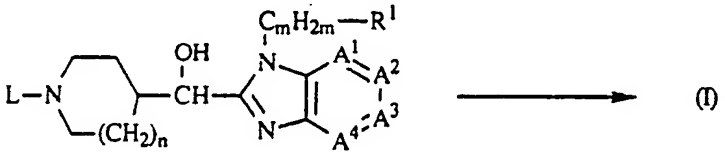


(d-4),

wherein Alk is C_{1-4}alkanediyl; and G^2 is -CH=CH-CH=CH-, -S-$(CH_2)_2$- or -S-CH=CH-.

The most interesting compounds are those interesting compounds wherein $-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula -CH=CH-CH=CH- (a-1) or -CH=CH-CH=N- (a-5); R^1 is 4-fluorophenyl; and G^2 is -CH=CH-CH=CH- or -S-$(CH_2)_2$-.

The compounds of formula (I) can generally be prepared by oxidizing the corresponding alcohol derivatives of formula (II) with suitable oxidizing agents in a reaction-inert solvent.



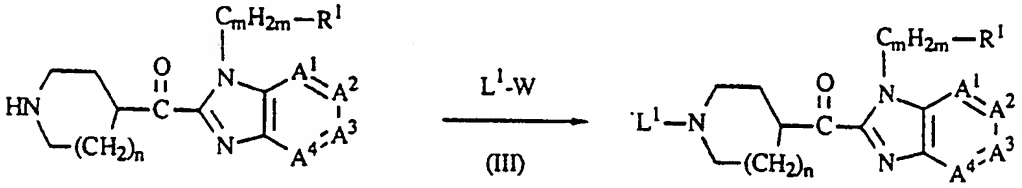
(II) (I)

Suitable oxidizing agents are for example several activated forms of manganese-(IV)oxide; selenium(IV)oxide; nickel(IV)oxide; ruthenium(IV)oxide; potassium permanganate; acid dichromate (various forms of chromic acid and of chromium(VI) oxide can be used); pyridine dichromate complex, e.g. poly(4-ethenylpyridinium-dichromate), pyridinium chlorochromate (PCC), pyridinium dichromate (PDC) (Collin's reagent); sodium dichromate; a mixture of sodium dichromate and sulfuric acid in dimethyl sulfoxide; a solution of chromic acid and sulfuric acid in 2-propanone (Jones' reagent); 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ); lead(IV)acetate; palladium(II)-acetate; N-bromo-acetamide; ceriumtrihydroxyhydroperoxide; and the like. Additionally, it may be advantageous to add extra air oxygen to the reaction mixture.

Suitable solvents for said oxidation reaction are, for example, water; a mixture of water and alkali (e.g. sodium hydroxide); hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene, chlorobenzene, dichloromethane, trichloromethane and the like; ketones, e.g. 2-propanone, 2-butanone, and the like; ethers, e.g. tetrahydrofuran, 1,4-dioxane and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, dimethyl sulfoxide, N,N-dimethylacetamide, acetonitrile, nitrobenzene, 1-methyl-2-pyrrolidinone and the like.

The compounds of formula (I) can also be obtained by catalytic dehydrogenation of the alcohol derivatives of formula (II). Examples of such dehydrogenation catalysts are copper chromite, copper, silver and the like. The reaction can be carried out in a reaction-inert solvent, like water; a hydrocarbon, e.g. methylbenzene, dichloromethane; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like.

The compounds of formula (I) wherein L is other than hydrogen, said L being represented by L^1, and said compounds being represented by formula (I-a) can be prepared by N-alkylating a compound of formula (I) wherein L is hydrogen, said compound being represented by (I-b), with an alkylating reagent of formula (III).



(I-b) (I-a)

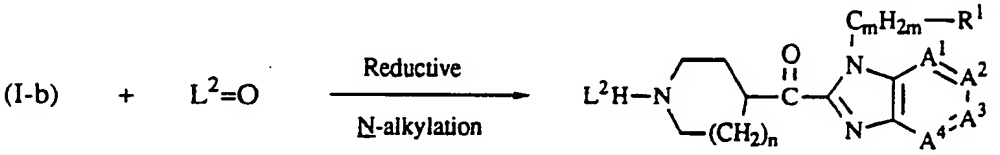
In formula (III) and hereinafter W represents an appropriate leaving group such as, for example, halo, e.g. chloro, bromo and the like; or a sulfonyloxy group such as, for example, methanesulfonyloxy, 4-methylbenzenesulfonyloxy and the like.

Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, water; an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction.

Additionally, it may be advantageous to conduct said N-alkylation under an inert atmosphere such as, for example, oxygen-free argon or nitrogen.

Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions. Said conditions comprise stirring the reactants with an appropriate base and optionally under an inert atmosphere as described hereinabove, in the presence of a suitable phase transfer catalyst such as, for example, a trialkylphenylmethylammonium, tetraalkylammonium, tetraalkylphosphonium, tetraarylphosphonium halide, hydroxide, hydrogen sulfate and the like catalysts.

The compounds of formula (I-a) wherein L is C_{1-12}alkyl, C_{3-6}cycloalkyl, a radical of formula (b-1), (b-2) or (b-3), said radicals being represented by the radical L^2H- and said compounds by formula (I-a-1) can also be prepared by the reductive N-alkylation reaction of (I-b) with an appropriate ketone or aldehyde of formula L^2=O (IV), said L^2=O being an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms are replaced by =O, and L^2 is a geminal bivalent radical comprising C_{1-12}alkylidene, C_{3-6}cycloalkylidene, R^3-C_{1-6}alkylidene, R^4-Y-C_{1-6}alkylidene and R^5-Z^2-C(=X)-Z^1-C_{1-6}alkylidene.

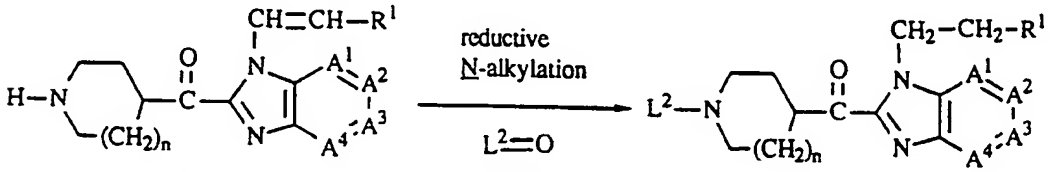


(IV) (I-a-1)

Said reductive N-alkylation reaction may conveniently be carried out by reducing a mixture of the reactants in a suitable reaction-inert solvent following art-known reductive N-alkylation procedures. In particular, the reaction mixture may be stirred and/or heated in order to enhance the reaction rate. Suitable solvents are, for example, water; C_{1-6}alkanols, e.g. methanol, ethanol, 2-propanol and the like; esters, e.g. ethyl acetate, γ-butyrolactone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybis-ethane, 2-methoxyethanol and the like; halogenated hydrocarbons, e.g. dichloro-methane, trichloromethane and the like; dipolar aprotic solvents, e.g. N,N-dimethyl-formamide, dimethyl sulfoxide and the like; carboxylic acids, e.g. acetic acid, propanoic acid and the like; or a mixture of such solvents. The term "art-known reductive N-alkylation procedures" means that the reaction is carried out either with sodium cyanoborohydride, sodium borohydride, formic acid or a salt thereof, e.g. ammonium formate and the like reducing agents, or alternatively under hydrogen atmosphere, optionally at an increased temperature and/or pressure, in the presence of an appropriate

catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene, quinoline-sulphur and the like. In some instances it may also be advantageous to add an alkali metal salt to the reaction mixture such as, for example, potassium fluoride, potassium acetate and the like salts.

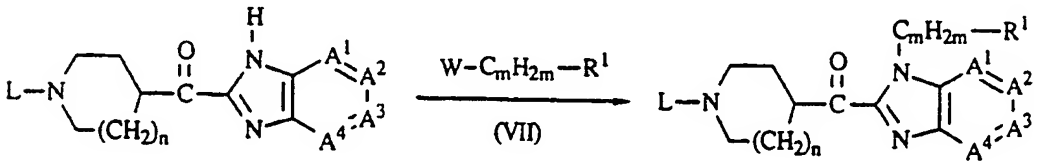
The compounds of formula (I-a-1) wherein m represents 2, said compounds being represented by formula (I-a-2) can also be prepared from an intermediate of formula (V)



(V) (I-a-2)

by reductive N-alkylation with an appropriate ketone or aldehyde L^2=O (IV) and simultaneous reduction of the alkene group. Said reaction can conveniently be conducted following the catalytic procedure described hereinbefore for preparing the compounds of formula (I-a-1) from the compounds of formula (I-b).

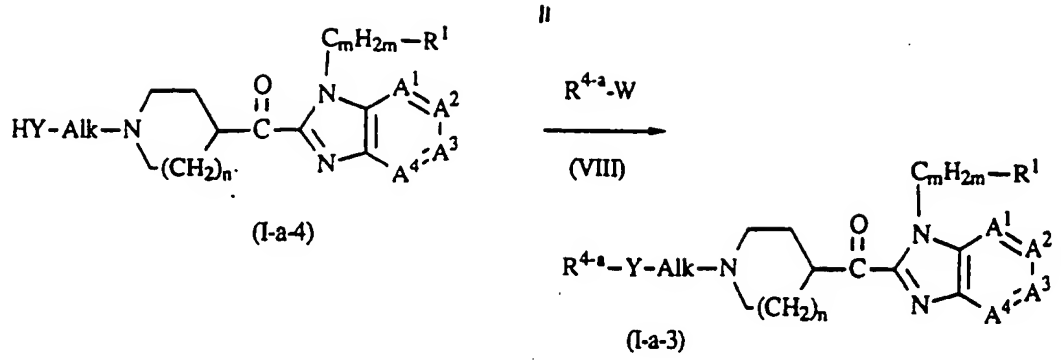
The compounds of formula (I) can also be prepared by N-alkylating an intermediate of formula (VI) with an appropriate alkylating reagent of formula (VII).



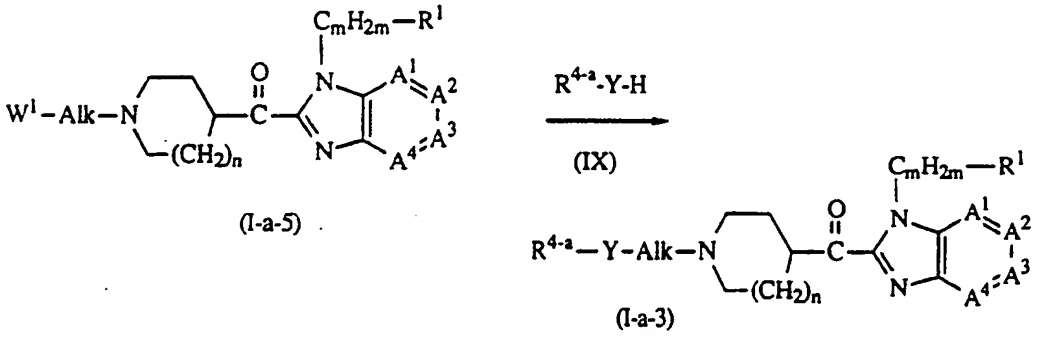
(VI) (I)

Said N-alkylation is conveniently conducted following art-known N-alkylation procedures as described hereinabove for the preparation of (I) from (I-b) and (III).

The compounds of formula (I) wherein L is a radical of formula (b-2) and R^4 is aryl or Het, said R^4 being represented by R^{4-a} and said compounds by formula (I-a-3) may also be prepared by alkylating a compound of formula (I) wherein L is a radical of formula (b-2) and R^4 is hydrogen, said compound being represented by formula (I-a-4), with a reagent of formula (VIII).

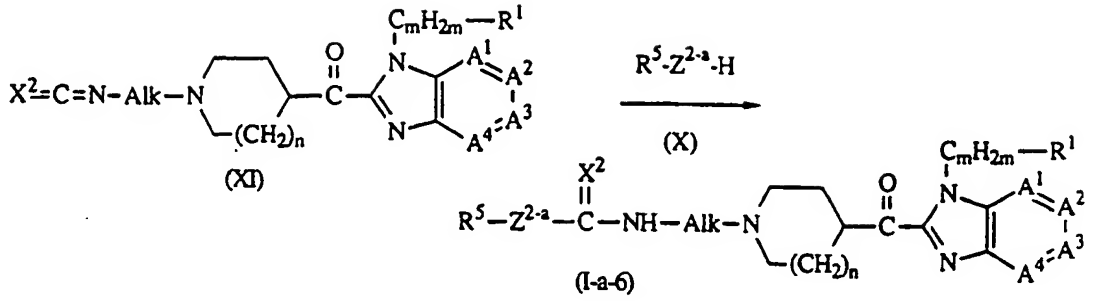


Similarly, the compounds of formula (I-a-3) may also be prepared by treating a compound of formula (I-a-5) with a reagent of formula (IX).



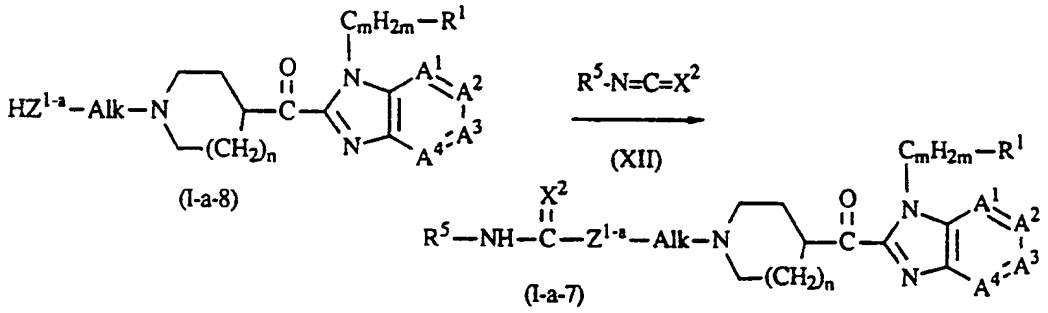
The alkylation reactions of (I-a-4) with (VIII) and (IX) with (I-a-5) may conveniently be conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran; and a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone, and the like. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. Somewhat elevated temperatures may enhance the rate of the reaction.

The compounds of formula (I) wherein L is a radical of formula (b-3), Z^1 is NH, Z^2 is other than a direct bond and X is other than NR^9, said Z^2 and X being represented by Z^{2-a} and X^2, and said compounds by (I-a-6), can be prepared by reacting an isocyanate (X^2 = O) or isothiocyanate (X^2 = S) of formula (XI) with a reagent of formula (X).



(XI) (X) (I-a-6)

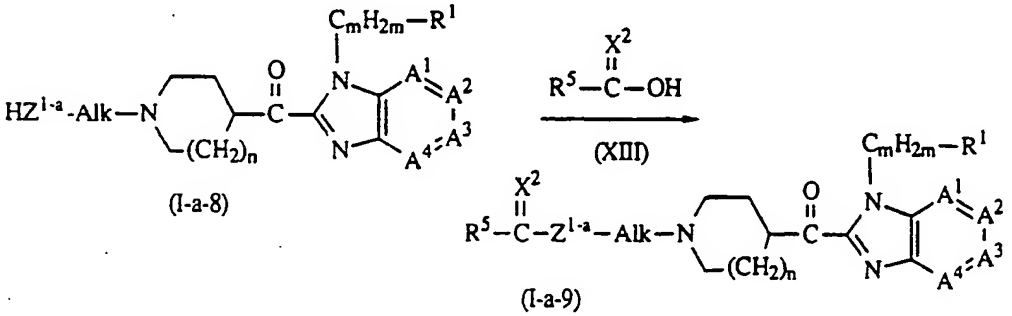
The compounds of formula (I) wherein L is a radical of formula (b-3), Z^2 is NH, Z^1 is other than a direct bond and X is other than NR^9, said Z^1 and X being represented by Z^{1-a} and X^2, and said compounds by (I-a-7), can be prepared by reacting an isocyanate (X^2 = O) or isothiocyanate (X^2 = S) of formula (XII) with a compound of formula (I-a-8).



(I-a-8) (XII) (I-a-7)

The reaction of (X) with (XI), or (XII) with (I-a-8) can generally be conducted in a suitable reaction-inert solvent such as, for example, an ether, e.g., tetrahydrofuran and the like, a halogenated hydrocarbon, e.g., trichloromethane and the like. Elevated temperatures may be suitable to enhance the rate of the reaction.

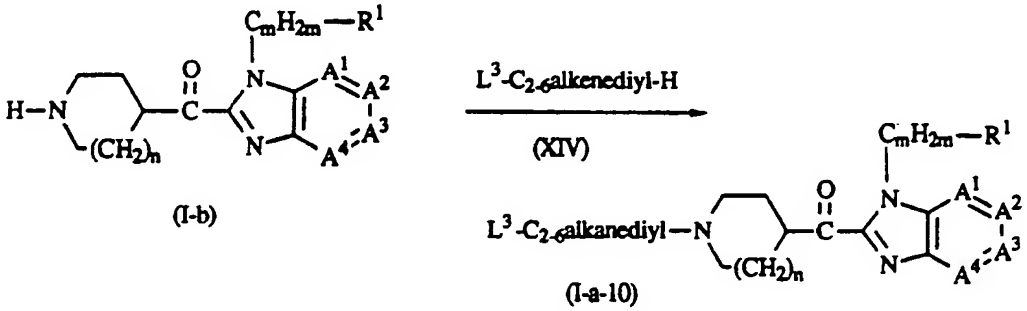
The compounds of formula (I) wherein L is a radical of formula (b-3), Z^2 is a direct bond, Z^1 is other than a direct bond and X is other than NR^9, said Z^1 and X being represented by Z^{1-a} and X^2, said compounds being represented by (I-a-9), can be prepared by reacting a compound of formula (I-a-8) with a reagent of formula (XIII) or a reactive functional derivative thereof.



(I-a-8) (XIII) (I-a-9)

The reaction of (XIII) with (I-a-8) may generally be conducted following art-known esterification or amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g., an anhydride or a carboxylic acid halide, which subsequently is reacted with (I-a-8); or by reacting (XIII) and (I-a-8) with a suitable reagent capable of forming amides or esters, e.g., N,N-methanetetraylbis[cyclohexanamine], 2-chloro-1-methylpyridinium iodide and the like. Said reactions may most conveniently be conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane, a dipolar aprotic solvent and the like. The addition of a base such as, for example, N,N-diethylethanamine and the like may be appropriate.

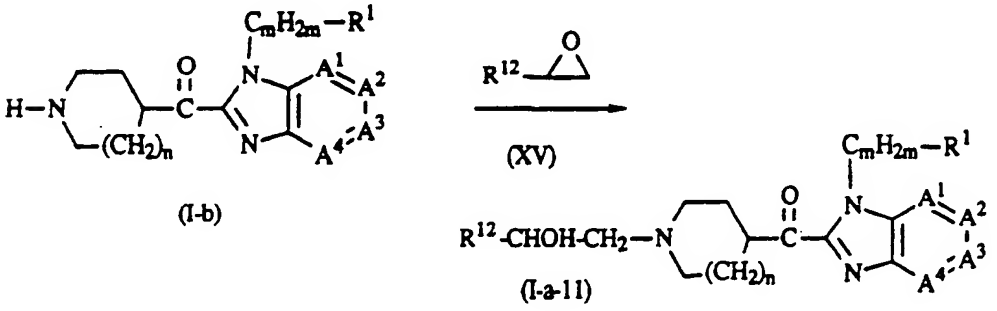
The compounds of formula (I) wherein L is a radical of formula L^3-C_{2-6}alkanediyl, said L^3 being aryl, Het or a radical of formula R^5-Z^2-C(=X)-, and said compounds being represented by formula (I-a-10), may also be prepared by the addition reaction of a compound of formula (I-b) to an appropriate alkene of formula (XIV).



(I-b)

(I-a-10)

The compounds of formula (I) wherein L is 2-hydroxy-C_{2-6}alkyl, 2-aryl-2-ethanol or a radical of formula (b-4), said compounds being represented by formula (I-a-II), can be prepared by reacting a compound of formula (I-b) with an epoxide (XV) wherein R^{12} is hydrogen, C_{1-4}alkyl, aryl or a radical R^6-O-CH_2-.



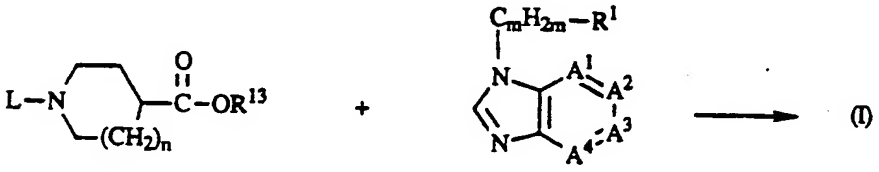
(I-b)

(I-a-11)

The reaction of (I-b) with respectively (XIV) and (XV) may be conducted by stirring and, if desired, heating the reactants in a reaction-inert solvent such as, for example, a ketone, e.g., 2-propanone, 4-methyl-2-pentanone, an ether, e.g., tetrahydrofuran, 1,1'-oxybisethane, an alcohol, e.g., methanol, ethanol, 1-butanol, a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like.

The compounds of formula (I) wherein L is a radical of formula (b-5) may be prepared by reducing the corresponding ketone compound of formula (I) wherein L is a radical of formula (b-3), Z^1 and Z^2 are direct bonds, X is O and R^5 is aryl, following art-known selective ketone-to-alcohol reduction procedures.

The compounds of formula (I) can also be obtained by conducting an acylation reaction between a piperidinyl derivative of formula (XVI) and a benzimidazole or a derivative thereof of formula (XVII) in a reaction-inert solvent. In formula (XVI) R^{13} represents a C_{1-6}alkyl group. Said acylation reaction is carried out in an appropriate reaction-inert solvent in the presence of a suitable strong base to obtain the salt form of formula (XVII), which reacts with the ester group of formula (XVI) to a compound of formula (I).



(XVI) (XVII)

Suitable strong bases are, for example, potassium tert. butoxide, n. butyllithium, sodium amide, sodium hydride or lithium diisopropylamide. Appropriate reaction-inert solvents are, for example, ethers, e.g. tetrahydrofuran, 1,4-dioxane and the like.

The compounds of formula (I) wherein R^3, R^4 or R^5 are Het, may also be prepared following art-known procedures for preparing heterocyclic ring systems or following analogous methods. A number of such cyclization procedures are described in for example, US-4,695,575 and in the references cited therein, in particular US-4,335,127; 4,342,870 and 4,443,451.

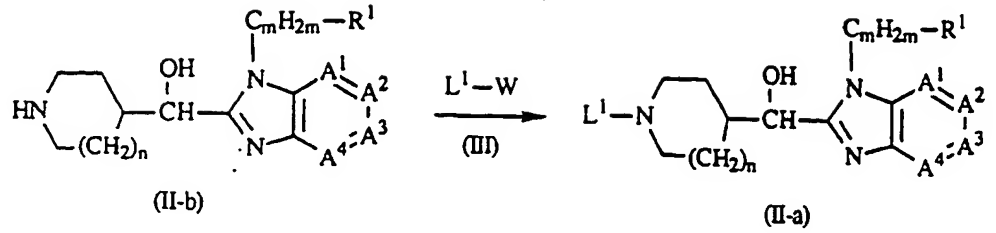
The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation. Some examples of such procedures are cited hereinafter. The compounds of formula (I) containing a cyano substituent can be converted into the corresponding amines by stirring and, if desired, heating the

starting cyano compounds in a hydrogen containing medium in the presence of an appropriate catalyst such as, for example, platinum-on-charcoal, Raney nickel and the like catalysts. Suitable solvents are, for example, methanol, ethanol and the like. The compounds of formula (I) containing an amino group can also be obtained by hydrolysis of the corresponding carbamate derivative in acidic medium. Amino groups may be alkylated or acylated following art-known procedures such as, for example, N-alkylation, N-acylation, reductive N-alkylation and the like methods. The compounds of formula (I) containing an amino group substituted with an arylmethyl radical, may be hydrogenolyzed by treating the starting compound with hydrogen in the presence of a suitable catalyst, e.g., palladium-on-charcoal, platinum-on-charcoal and the like, preferably in an alcoholic medium. The compounds of formula (I) wherein L is methyl or phenylmethyl can be converted into compounds of formula (I) wherein L is a C_{1-6}alkyloxycarbonyl group by reacting the methyl or phenylmethyl derivative with C_{1-6}alkyloxycarbonyl halides such as, for example, ethyl chloroformate in a suitable reaction-inert solvent and in the presence of a base like N,N-diethylethanamine. The compounds of formula (I-b) wherein L is hydrogen can be obtained from compounds of formula (I) wherein L is phenylmethyl or C_{1-6}alkyloxycarbonyl following art-known procedures like catalytic hydrogenation or hydrolysis in an acidic or alkaline medium depending on the nature of L.

In all of the foregoing and in the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

Some intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds. The hydroxymethylene derivatives of formula (II) are new and are especially developed for the preparation of the compounds of formula (I). A number of the preparation methods, in particular for said novel intermediates, is described hereinafter in more detail.

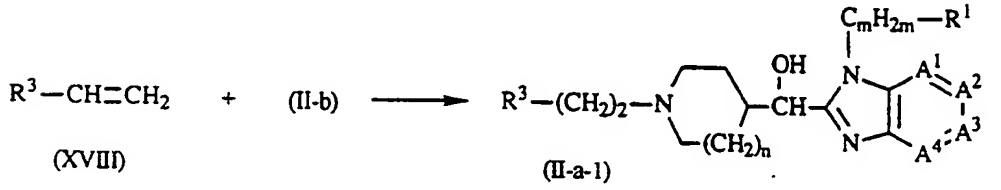
The intermediates of formula (II), wherein L is other than H, said L being represented by L^1, and said intermediates by formula (II-a) can be prepared by N-alkylating an intermediate of formula (II) wherein L is H, said intermediate being represented by (II-b), with an alkylating reagent of formula (III).



(II-b) (III) (II-a)

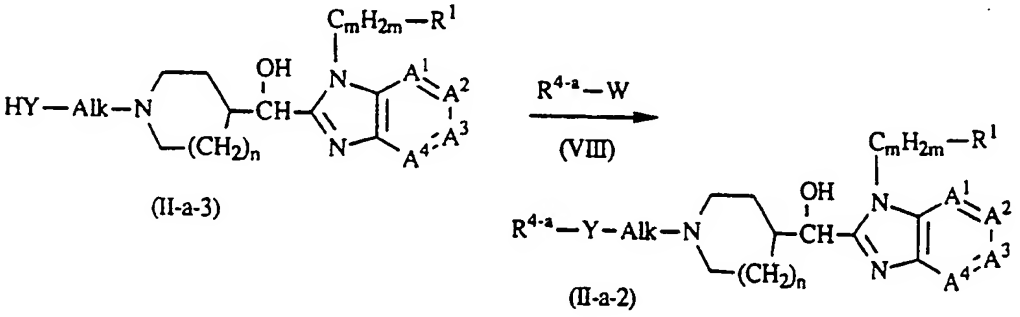
Said N-alkylation is conveniently conducted following art-known N-alkylation procedures as described hereinabove for the preparation of (I) from (I-b) and (III).

The intermediates of formula (II), wherein L is a radical of formula R^3-$(CH_2)_2$-, said intermediates being represented by formula (II-a-1) can be prepared by alkylating a piperidine of formula (II-b) with an alkene derivative of formula (XVIII). Said reaction can be carried out in, for example, aromatic hydrocarbons, e.g. benzene, methylbenzene, and the like; alkanols, e.g. methanol, ethanol, 2-propanol, 1-butanol and the like; ketones, e.g. 2-propanone and the like; ethers, e.g. tetrahydrofuran and the like, or mixtures of such solvents.



(XVIII) (II-b) (II-a-1)

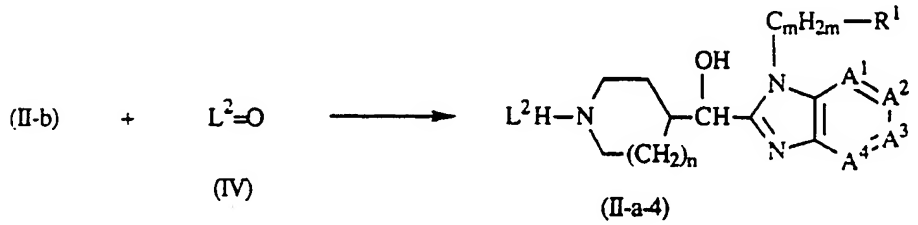
The intermediates of formula (II) wherein L is a radical of formula (b-2) and R^4 is aryl or Het, said R^4 being represented by R^{4-a} and said intermediates by formula (II-a-2) may also be prepared by alkylating an intermediate of formula (II) wherein L is a radical of formula (b-2) and R^4 is H, said intermediates being represented by formula (II-a-3), with a reagent of formula (VIII).



(II-a-3) (VIII) (II-a-2)

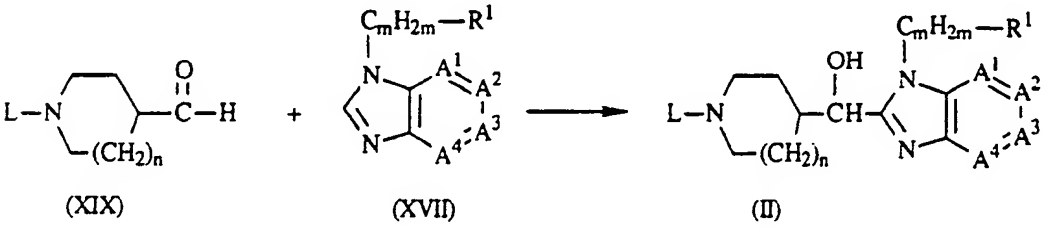
The alkylation reaction may conveniently be conducted as described for the preparation of (I-a-3) from (I-a-4) and (VIII).

The intermediates of formula (II-a) wherein L is C_{1-12}alkyl, C_{3-6}cycloalkyl, a radical of formula (b-1), (b-2) or (b-3), said radical being represented by the radical L^2H- and said intermediates by (II-a-4) can also be prepared by the reductive N-alkylation reaction of (II-b) with an appropriate ketone or aldehyde of formula L^2=O (IV) as defined hereinbefore.



The reaction can be carried out as described for the preparation of (I-a-1) from (I-b) and (IV).

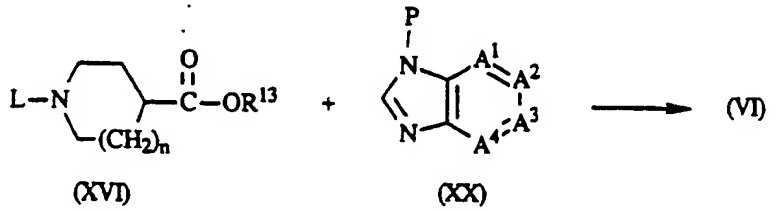
The intermediates of formula (II) can also be obtained by acylating an intermediate of formula (XVII) with an aldehyde of formula (XIX) in a reaction-inert solvent. The reaction is carried out in the presence of a suitable base as described for the preparation of (I) from (XVI) and (XVII).



The intermediates of formula (II) can also be converted into each other following art-known procedures of functional group transformation as described hereinbefore for the compounds of formula (I).

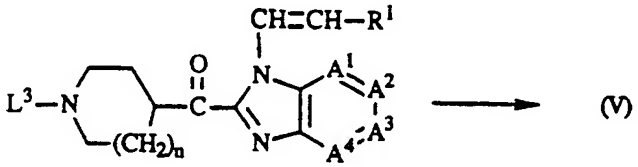
The intermediates of formula (VI) can be prepared by conducting an acylation reaction between a piperidinyl derivative of formula (XVI) and a protected fused imidazole of formula (XX) in a reaction-inert solvent. In formula (XX) P represents for example, di(C_{1-4}alkyloxy)methyl. Said acylation reaction is carried out by preparing a salt form of the compound of formula (XX) with a strong base (as described hereinbefore for intermediate (XVII)), reacting said salt form with the ester (XVI) and

subsequently hydrolyzing the protective group P in the thus obtained product by acid hydrolysis e.g. with acetic acid and the like.



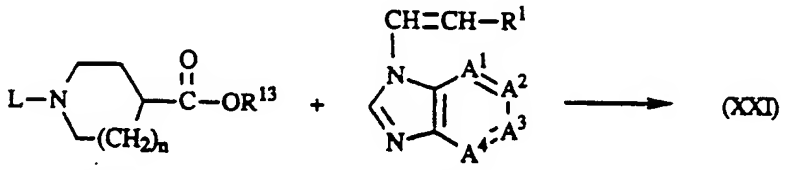
(XVI) (XX) (VI)

The intermediates of formula (V) can be obtained from compounds of formula (XXI), wherein L is C_{1-6}alkyloxycarbonyl, said L being represented by L^3, following art-known procedures such as hydrolysis in an acidic or alkaline medium.



(XXI) (V)

The intermediates of formula (XXI) can be prepared from a piperidinyl derivative of formula (XVI) and a fused imidazole of formula (XXII) in a reaction-inert solvent as described hereinbefore for the preparation of the compounds of formula (VI).



(XVI) (XXII) (XXI)

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like; and enantiomers may be separated from each other following art-known resolution methods, for example, by the selective crystallization of their diastereomeric salts with chiral acids. Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reactions occur stereospecifically. Preferably, if a specific stereoisomer is desired, said

compound will be synthesized by stereoselective methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof possess useful pharmacological properties. More particularly, they are active antihistaminics which can clearly be demonstrated by, e.g., the results obtained in the test "Protection of Rats from Compound 48/80-induced lethality".

In view of their antihistaminic properties, the compounds of formula (I) and their acid addition salts are very useful in the treatment of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

In view of their useful antihistaminic properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antihistaminic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any

nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an antiallergically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt form thereof.

Those of skill in treating allergic diseases in warm-blooded animals could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an antiallergically effective amount would be from about 0.001 mg/kg to about 20 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 5 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

Experimental Part

A. Preparation of the intermediates

Example 1

A mixture of 103 parts of N^1-[(5-methyl-2-furanyl)methyl]-1,2-benzenediamine, 450 parts of [[bis(ethoxy)]methoxy]ethane and 10 drops of concentrated HCl was stirred for 1 hour at 100°C. The reaction mixture was evaporated and the residue was taken up in 4-methyl-2-pentanone. This solution was washed with water, dried, filtered and

evaporated. The residue was stirred with activated charcoal in 2,2'-oxybispropane. The whole was filtered and the filtrate was evaporated. The residue was crystallized from 2,2'-oxybispropane, yielding 61.5 parts (59.1%) of 1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazole (interm. 1).

In a similar manner there were also prepared :

3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridine (interm. 2); and

3-[(4-fluorophenyl)methyl]-3H-imidazo[4,5-b]pyridine (interm. 3).

Example 2

A mixture of 154 parts of N^3-[(4-fluorophenyl)methyl]-2,3-pyridinediamine, 800 parts of [[bis(ethoxy)]methoxy]ethane and 10 drops of concentrated HCl was stirred for 1 hour at 100°C. The reaction mixture was evaporated and the residue was taken up in 4-methyl-2-pentanone. This solution was washed with water, dried, filtered and evaporated. The residue was crystallized from 1,1'-oxybisethane. The product was filtered off and dried, yielding 140.8 parts (88.5%) of 1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-b]pyridine (interm. 4).

Example 3

a) A mixture of 29.0 parts of N^2-(2-ethoxyethyl)-2,3-pyridinediamine and 14.6 parts of α-hydroxyacetic acid was stirred for 3 hours in vacuo at 175°C. The reaction mixture was taken up in a mixture of trichloromethane and methanol and the whole was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2,2'-oxybispropane by the addition of 2-propanol saturated with HCl. The salt was recrystallized from acetonitrile (2x). The product was filtered off and dried, yielding 19.7 parts (47.7%) of 3-(2-ethoxyethyl)-3H-imidazo[4,5-a]pyridine-2-methanol monohydrochloride; mp. 158.3°C (interm. 5).

b) To a stirred solution of 6.2 parts of intermediate 5 in 75 parts of trichloromethane there were added 27.5 parts of thionyl chloride. After stirring for 1 1/2 hour at reflux temperature, the reaction mixture was evaporated and the residue was triturated in methylbenzene. The product was filtered off and dried, yielding 3.35 parts (50.5%) of 2-(chloromethyl)-3-(2-ethoxyethyl)-3H-imidazo[4,5-a]pyridine monohydrochloride (interm. 6).

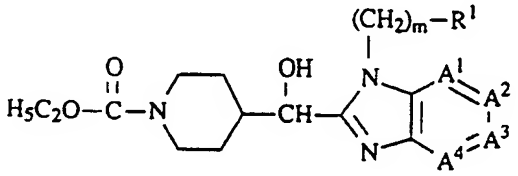
Example 4

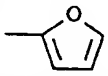
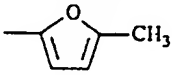
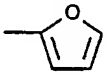
To a stirred and cooled (-70°C) mixture of 33.8 parts of N-(1-methylethyl)-2-propanamine and 338 parts of tetrahydrofuran there were added 90 parts of a 1-butyllithium solution in hexane 2.5 M in 3 portions, keeping the temperature below -60°C. After

stirring for 15 min at -60/-70°C, there was added dropwise a solution of 61.7 parts of intermediate 1 in 112 parts of tetrahydrofuran. Stirring was continued for 1 hour and then there were added dropwise 59.3 parts of ethyl 4-formyl-1-piperidinecarboxylate. At room temperature, the reaction mixture was diluted with water and extracted with trichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; $CHCl_3$ / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile (2x), yielding 33.2 parts (28.8%) of ethyl 4-[hydroxy[1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl]methyl]-1-piperidinecarboxylate; mp. 174.3°C (interm. 9).

The other intermediates listed in Table 1 were prepared following the above described method.

Table 1



Int. No.	m	R^1	$-A^1=A^2-A^3=A^4-$	physical data (mp.)
7	1		-CH=CH-CH=CH-	-
8	1	4-F-C_6H_4-	-N=CH-CH=CH-	-
9	1		-CH=CH-CH=CH-	174.3°C
10	1		-N=CH-CH=CH-	-
11	1	4-F-C_6H_4-	-CH=CH-CH=N-	-
12	2	C_6H_5-	-CH=CH-CH=CH-	-

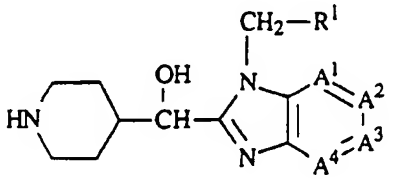
Example 5

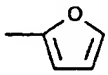
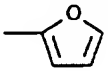
A mixture of 90 parts of intermediate 8; 126 parts of potassium hydroxide, 20 parts of water and 1200 parts of 2-propanol was stirred overnight at reflux temperature. After cooling, the reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was taken up in dichloromethane and this solution was washed with water, dried, filtered and evaporated. The residue was crystallized from acetonitrile,

yielding 43.5 parts (60.8%) of 3-[(4-fluorophenyl)methyl]-α-(4-piperidinyl)-3H-imidazo[4,5-b]pyridine-2-methanol; mp. 204.8°C (interm. 13).

The other intermediates listed in Table 2 were prepared following the above described method.

Table 2



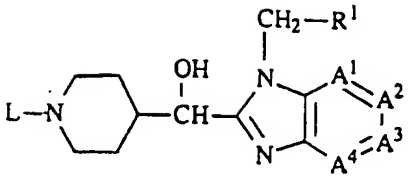
Int. No.	R^1	$-A^1=A^2-A^3=A^4-$	physical data
13	4-F-C_6H_4-	-N=CH-CH=CH-	204.8°C
14		-CH=CH-CH=CH-	166.5°C
15		-N=CH-CH=CH-	-
16	4-F-C_6H_4-	-CH=CH-CH=N-	212.9°C
17		-CH=CH-CH=CH-	151.1°C

Example 6

A mixture of 8.5 parts of 1-(2-chloroethyl)-4-methoxybenzene, 10.2 parts of intermediate 16; 5.3 parts of sodium carbonate and 135 parts of N,N-dimethylformamide was stirred overnight at 70°C. The reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was purified twice by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 95:5 ; $CHCl_3$ / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The product was filtered off and dried, yielding 1.9 parts (5.3%) of 1-[(4-fluorophenyl)methyl]-α-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1H-imidazo[4,5-b]pyridine-2-methanol (E)-2-butenedioate (1:2); mp. 188.4°C (interm. 29).

The other intermediates listed in Table 3 were prepared following the above described method.

Table 3



Int. No.	L	R^1	$-A^1=A^2-A^3=A^4-$	physical data
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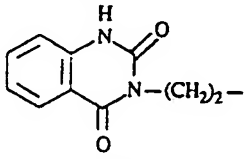
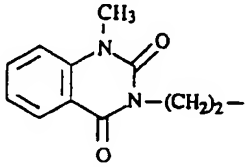
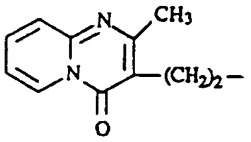
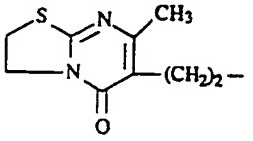
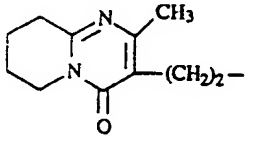
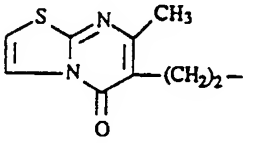
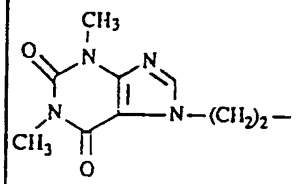
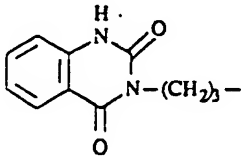
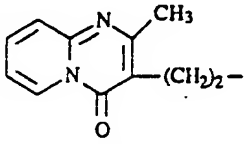
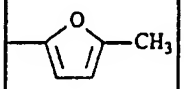
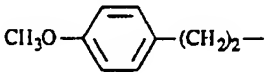
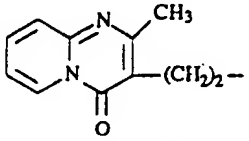
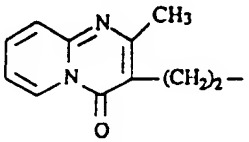
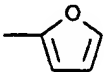
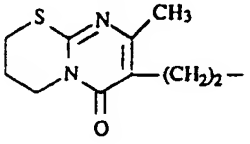
19		4-F-C_6H_4-	-CH=CH-CH=CH-	178.9°C
20		4-F-C_6H_4-	-CH=CH-CH=CH-	141.6°C / H_2O / 2.5 (E)-2-butenedioate
21		4-F-C_6H_4-	-CH=CH-CH=CH-	216.1°C/2$(COOH)_2$
22		4-F-C_6H_4-	-CH=CH-CH=CH-	201.0°C/2$(COOH)_2$
23		4-F-C_6H_4-	-CH=CH-CH=CH-	197.8°C/2$(COOH)_2$
24		4-F-C_6H_4-	-CH=CH-CH=CH-	196.4°C/2$(COOH)_2$
25		4-F-C_6H_4-	-CH=CH-CH=CH-	147.9°C

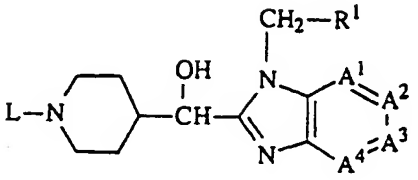
Int. No.	L	R^1	$-A^1=A^2-A^3=A^4-$	physical data
26		4-F-C_6H_4-	-CH=CH-CH=CH-	203.8°C
27	NC-CH_2-	4-F-C_6H_4-	-CH=CH-CH=N-	168.1°C
28			-CH=CH-CH=CH-	-
29		4-F-C_6H_4-	-CH=CH-CH=N-	188.4°C / 2 (E)-2-butenedioate
30		4-F-C_6H_4-	-CH=CH-CH=N-	-
31			-N=CH-CH=CH-	-
32		4-F-C_6H_4-	-CH=CH-CH=N-	134.8°C

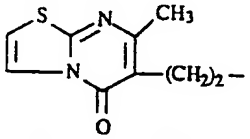
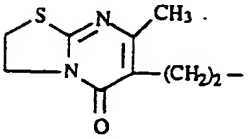
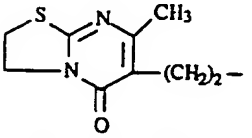
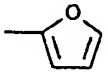
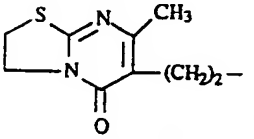
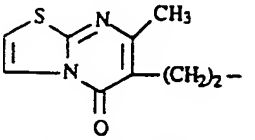
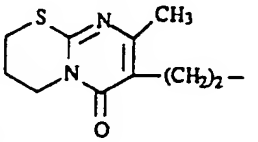
Example 7

A mixture of 7 parts of 6-(2-bromoethyl)-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]-pyrimidin-5-one monohydrobromide; 8 parts of intermediate 17; 3.2 parts of sodium carbonate and 160 parts of 4-methyl-2-pentanone was refluxed over weekend. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 8.2 parts (64.7%) of 6-[2-[4-[[3-(2-furanylmethyl)-3H-imidazo[4,5-b]pyridin-2-yl]hydroxymethyl]-1-piperidinyl]ethyl]-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 129.4°C (interm. 35).

The other intermediates listed in Table 4 were prepared following the above described method.

Table 4



Int. No.	L	R^1	$-A^1=A^2-A^3=A^4-$	physical data
33		4-F-C_6H_4-	-CH=CH-CH=N-	211.0°C
34		4-F-C_6H_4-	-CH=CH-CH=N-	178.0°C
35			-N=CH-CH=CH-	129.4°C
36			-CH=CH-CH=CH-	171.5°C
37			-CH=CH-CH=CH-	116.4°C/ 1/2H_2O
38		4-F-C_6H_4-	-CH=CH-CH=CH-	-

Example 8

A mixture of 6.0 parts of 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one, 4.0 parts of 1-[(4-fluorophenyl)methyl]-α-(4-piperidinyl)-1H-benzimidazole-2-methanol (described in EP-A-0,363,963), 2.5 parts of N,N-diethylethanamine and 45 parts of N,N-dimethylformamide was stirred overnight at 50°C. The reaction mixture was

evaporated and the residue was diluted with Na_2CO_3 5%. The product was extracted with trichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 96:4). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:2) salt in ethanol. The solution was evaporated and the residue was recrystallized from a mixture 2-propanone and some ethanol, yielding 5.9 parts (48.0%) of 1-[3-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]hydroxymethyl]-1-piperidinyl]propyl]-1,3-dihydro-2H-benzimidazol-2-one ethanedioate (1:2); mp. 168.0°C (interm. 39).

Example 9

A mixture of 5.11 parts of 2-ethenylpyridine, 1.74 parts of intermediate 16 and 120 parts of 1-butanol was stirred overnight at reflux temperature. The reaction mixture was left over weekend and was then evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated, yielding 4 parts (59.8%) of 1-[(4-fluorophenyl)methyl]-α-[1-[2-(2-pyridinyl)ethyl]-4-piperidinyl]-1H-imidazo[4,5-b]pyridine-2-methanol (interm. 40).

In a similar manner there was also prepared :

1-(2-furanylmethyl)-α-[1-[2-(2-pyridinyl)ethyl]-4-piperidinyl]-1H-benzimidazole-2-methanol (interm. 41).

Example 10

A mixture of 10.2 parts of intermediate 16; 15 parts of a formaldehyde solution 37% and 18 parts of formic acid was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NH_4OH, the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated, yielding 9 parts (32.6%) of 1-[(4-fluorophenyl)methyl]-α-(1-methyl-4-piperidinyl)-1H-imidazo[4,5-b]pyridine-2-methanol (interm. 42).

In a similar manner there was also prepared :

1-[(5-methyl-2-furanyl)methyl]-α-(1-methyl-4-piperidinyl)-1H-benzimidazole-2-methanol (interm. 43).

Example 11

A mixture of 3.75 parts of intermediate 15; 2 parts of polyoxymethylene, 2 parts of a solution of thiophene in methanol 4% and 120 parts of methanol was hydrogenated at normal pressure and room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off

and the filtrate was evaporated. The residue was dissolved in dichloromethane and this solution was washed with NH_4OH (dil.) and water (2x), dried, filtered and evaporated. The residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 3.2 parts (81.6%) of 3-(2-furanylmethyl)-α-(1-methyl-4-piperidinyl)-3H-imidazo[4,5-b]pyridine-2-methanol; mp. 146°C (interm. 44).

In a similar manner there were also prepared :

1-[(4-fluorophenyl)methyl]-α-(1-methyl-4-piperidinyl)-1H-benzimidazole-2-methanol (E)-2-butenedioate (2:3); mp. 171.9°C (interm. 45); and

1-(2-furanylmethyl)-α-(1-methyl-4-piperidinyl)-1H-benzimidazole-2-methanol (interm. 46).

Example 12

A mixture of 9 parts of intermediate 27 and 240 parts of methanol saturated with NH_3 was hydrogenated at normal pressure and 20°C with 3 parts of Raney nickel. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 10 parts (100%) of α-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-b]pyridine-2-methanol (interm. 47).

In a similar manner there was also prepared :

α-[1-(2-aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1H-benzimidazole-2-methanol (E)-2-butenedioate (2:5) (interm. 48).

Example 13

A mixture of 2.29 parts of 2-chloropyrimidine, 7.6 parts of intermediate 48; 2.1 parts of sodium hydrogen carbonate and 80 parts of ethanol was stirred overnight at reflux temperature. The reaction mixture was evaporated and the residue was diluted with water. The product was extracted with trichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 92:8). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:2) salt in ethanol. The salt was recrystallized from ethanol. The product was filtered off and dried, yielding 4 parts (31.2%) of 1-[(4-fluorophenyl)-methyl]-α-[1-[2-[(2-pyrimidinyl)amino]ethyl]-4-piperidinyl]-1H-benzimidazole-2-methanol ethanedioate (1:2); mp. 108.3°C (interm. 49).

In a similar manner there was also prepared :

1-[(4-fluorophenyl)methyl]-α-[1-[2-(2-pyrimidinylamino)ethyl]-4-piperidinyl]-1H-imidazo[4,5-b]pyridine-2-methanol; mp. 119.6°C (interm. 50).

Example 14

To a stirred mixture of 5.7 parts of intermediate 48 and 90 parts of tetrahydrofuran there was added dropwise a solution of 3.8 parts of methyl 2-isothiocyanatobenzoate in tetrahydrofuran. After stirring overnight at room temperature, the reaction mixture was evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was successively crystallized from acetonitrile and ethanol. The product was filtered off and dried, yielding 2 parts (24.5%) of 3-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]hydroxymethyl]-1-piperidinyl]ethyl]-2,3-dihydro-2-thioxo-4(1H)-quinazolinone; mp. 180.0°C (interm. 51).

Example 15

a) To a stirred and heated (50°C) mixture of 2.44 parts of 3,1-benzoxazine-2,4(1H)-dione and 45 parts of N,N-dimethylformamide there was added dropwise a solution of 5.7 parts of intermediate 48 in 45 parts of N,N-dimethylformamide. After stirring for 4 hours at 50°C, the reaction mixture was diluted with water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:2) salt in ethanol. The product was filtered off and dried, yielding 6 parts (59%) of 2-amino-N-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]hydroxymethyl]-1-piperidinyl]ethyl]benzamide ethanedioate (1:2); mp.173.6°C (interm. 52).

b) To a stirred mixture of 1.02 parts of acetic anhydride and 50 parts of water there were added portionwise 5 parts of intermediate 52. After stirring for 20 hours at 80-100°C, there were added crushed ice and NH_4OH. The product was extracted with trichloromethane and the extract was dried, filtered and evaporated. The residue was converted into the ethanedioate (1:2) salt in ethanol. The salt was recrystallized from methanol. The product was filtered off and dried, yielding 2.4 parts (34.0%) of 3-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]hydroxymethyl]-1-piperidinyl]-ethyl]-2-methyl-4(3H)-quinazolinone ethanedioate (1:2); mp. 240.2°C (interm. 53).

Example 16

To a stirred and cooled (-75°C) mixture of 10 parts of N-(1-methylethyl)-2-propanamine in 178 parts of tetrahydrofuran under nitrogen there were added dropwise 28.8 parts of a solution of n.butyllithium in hexane 2.5M. Stirring was continued for 1/2 hour at -60°C and for 15 min at -40°C. At -75°C, there was added dropwise a solution of 22 parts of 1-(diethoxymethyl)-1H-benzimidazole in 44.5 parts of tetrahydrofuran and, after stirring

for 2 hours, a solution of 25.7 parts of (1,1-dimethylethyl) 4-(ethoxycarbonyl)-1-piperidinecarboxylate in 44.5 parts of tetrahydrofuran. The whole was stirred for 1 hour at -75°C and was then left to reach room temperature overnight. The reaction mixture was diluted with 200 parts of ice-water and extracted with 266 parts of dichloromethane. The aqueous layer was re-extracted with dichloromethane (2x) and the organic layers were dried, filtered and evaporated. The residue was stirred for 1 hour in a mixture of acetic acid and water (1:3). The product was filtered off and dried, yielding 30.5 parts (92.6%) of 1,1-dimethyl 4-(1H-benzimidazol-2-ylcarbonyl)-1-piperidinecarboxylate (interm. 54).

Example 17

a) To a stirred and cooled (-70°C) mixture of 8.8 parts of cis-1-(2-phenylethenyl)-1H-benzimidazole and 89 parts of tetrahydrofuran under nitrogen there were added dropwise 10.9 parts of a solution of n. butyllithium in hexane and, after stirring for 1/2 hour at -70°C, a solution of 10.3 parts of (1,1-dimethylethyl) 4-(ethoxycarbonyl)-1-piperidinecarboxylate in some tetrahydrofuran. Stirring at -70°C was continued for 1 hour. At room temperture, the reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 97:3 → 94:6). The eluent of the desired fraction was evaporated and the residue was crystallized from a mixture of 2,2'-oxybispropane and acetonitrile. The product was filtered off and dried, yielding 7.0 parts (40.6%) of (1,1-dimethyl) (Z)-4-[[1-(2-phenylethenyl)-1H-benzimidazol-2-yl]carbonyl]-1-piperidinecarboxylate; mp. 155.8°C (interm. 55).

b) A mixture of 18.6 parts of intermediate 55 and 192.4 parts of trifluoroacetic acid was stirred for 1/2 hour at room temperature. The reaction mixture was poured into 1,1'-oxybisethane. The precipitate was filtered off, washed with 1,1'-oxybisethane and dried, yielding 18.0 parts (94.0%) of (Z)-[1-(2-phenylethyl)-1H-benzimidazol-2-yl] (4-piperidinyl)methanone trifluoroacetate (1:1); mp. 202.2°C (interm. 56).

In a similar manner there were also prepared:

[1-(phenylmethyl)-1H-benzimidazol-2-yl] (4-piperidinyl)methanone monohydrochloride; mp. 197.7°C (interm. 57)

[1-[2-(4-fluorophenyl)ethyl]-1H-benzimidazol-2-yl] (4-piperidinyl)methanone trifluoroacetate (1:2); 158.1°C (interm. 58).

B. Preparation of the final compounds

Example 18

A mixture of 3.4 parts of intermediate 30; 16 parts of manganese(IV)oxide and 133 parts of dichloromethane was stirred for 90 hours at room temperature. The reaction mixture was filtered over diatomaceous earth. The filtrate was washed with a mixture of

trichloromethane and methanol and then evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from 2,2'-oxybispropane and acetonitrile. The product was filtered off and dried, yielding 1.7 parts (49.8%) of 3-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-imidazo[4,5-b]pyridin-2-yl]carbonyl]-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 183.0°C (comp. 26).

Example 19

A mixture of 4 parts of intermediate 43; 6.5 parts of poly(4-ethenylpyridinium dichromate) and 135 parts of methylbenzene was stirred for 3 hours at reflux temperature. There were added 90 parts of tetrahydrofuran and the whole was filtered while hot over diatomaceous earth. The filtrate was evaporated and the residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:2) salt in acetonitrile. The product was filtered off and dried, yielding 1.5 parts (23.7%) of [1-[(5-methyl-2-furanyl)methyl]-1H-benzimidazol-2-yl] (1-methyl-4-piperidinyl)methanone ethanedioate (1:2) monohydrate; mp.124.0°C (comp. 22).

Example 20

To a stirred mixture of 13.2 parts of intermediate 54 and 235 parts of N,N-dimethylformamide under nitrogen there were added portionwise 2 parts of a dispersion of sodium hydride in mineral oil (50%). and, after stirring for 1 hour at room temperature, dropwise a solution of 10 parts of 5-bromomethyl-2-methyloxazole in 47 parts of N,N-dimethylformamide. Stirring at room temperature was continued for 1 hour. The reaction mixture was evaporated and the residue was taken up in dichloromethane. The whole was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 98:2). The eluent of the desired fraction was evaporated, yielding 19.6 parts (100%) of (1,1-dimethylethyl) 4-[[1-[(2-methyl-5-oxazolyl)methyl]-1H-benzimidazol-2-yl]carbonyl]-1-piperidine-carboxylate (comp. 44).

Example 21

A mixture of 19 parts of compound 44, 15.6 parts of 2-propanol saturated with HCl and 142.2 parts of methanol was stirred for 1 hour at reflux temperature. After cooling, the reaction mixture was evaporated. The residue was taken up in water and the whole was basified with NaOH 50% (aq.). The product was extracted with dichloromethane (3x) and the combined extracts were washed with water, dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / $CH_3OH(NH_3)$

90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (2:3) salt in 2-propanol. The salt was filtered off and dried, yielding 1.4 parts (7.0%) of [1-[(2-methyl-5-oxazolyl)methyl]-1H-benzimidazol-2-yl] (4-piperidinyl)methanone (E)-2-butenedioate (2:3); mp. 176.2°C (comp. 45).

Example 22

A mixture of 2.3 parts of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, 3.4 parts of compound 15; 1.6 parts of sodium carbonate and 90 parts of N,N-dimethylformamide was stirred overnight at 70°C. After cooling, the reaction mixture was poured into water and the whole was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; $CHCl_3$ / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1 part (19.0%) of 3-[2-[4-[[3-[(4-fluorophenyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-yl]carbonyl]-1-piperidinyl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 101.2°C (comp. 17).

Example 23

A mixture of 3.2 parts of 2,3-dihydro-1,4-benzodioxin-2-methanol 4-methyl-benzenesulfonate(ester), 4.3 parts of [1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl] (4-piperidinyl)methanone ethanedioate (1:1) (described in EP-A-0,363,963), 3.2 parts of sodium carbonate and 45 parts of N,N-dimethylformamide was stirred overnight at 70°C. The reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate salt in acetonitrile. The product was filtered off and dried, yielding 1.2 parts (21%) of [1-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-4-piperidinyl] [1-[(4-fluorophenyl)-methyl]-1H-benzimidazol-2-yl]methanone ethanedioate (1:1); mp. 178.6°C (comp. 13).

Example 24

A mixture of 3.7 parts of 6-(2-bromoethyl)-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]-pyrimidin-5-one monohydrobromide; 3.37 parts of [1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl] (4-piperidinyl)methanone, 3.0 parts of N,N-diethylethanamine and 90 parts of N,N-dimethylformamide was stirred overnight at 60°C. The reaction mixture was poured into water and the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 97:3). The eluent of the desired fraction was

evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.55 parts (29%) of 6-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]carbonyl]-1-piperidinyl]ethyl]-2,3-dihydro-7-methyl-5H-thiazolo-[3,2-a]pyrimidin-5-one; mp. 187.3°C (comp. 6).

Example 25

A mixture of 4 parts of intermediate 6; 6 parts of [1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl] (4-piperidinyl)methanone, 1.7 parts of sodium hydrogen carbonate and 79 parts of ethanol was refluxed overnight . The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was stirred in 2,2'-oxybispropane. The product was filtered off and dried, yielding 0.6 parts (6.5%) of [1-[[3-(2-ethoxyethyl)-3H-imidazo[4,5-b]pyridin-2-yl]methyl]-4-piperidinyl] [1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]methanone; mp. 141.0°C (comp. 32).

Example 26

A mixture of 3.38 parts of compound 15; 5 parts of a formaldehyde solution 40% and 6 parts of formic acid was stirred for 4 hours at 100°C. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NH_4OH, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, and the residue was purified by column chromatography (silica gel ; $CHCl_3$ / CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the ethanedioate (1:1) salt in acetonitrile. The product was filtered off and dried, yielding 1.3 parts (29.3%) of [3-[(4-fluorophenyl)methyl]-3H-imidazo[4,5-b]-pyridin-2-yl] (1-methyl-4-piperidinyl)methanone ethanedioate (1:1); mp. 206.2°C (comp. 16).

Example 27

A mixture of 4.95 parts of [1-(2-phenylethyl)-1H-benzimidazol-2-yl] (4-piperidinyl) methanone dihydrobromide (described in EP-A-0,363,963), 5 parts of potassium acetate, 2 parts of a solution of thiophene in methanol 4%, 2 parts of polyoxymethylene and 79 parts of methanol was hydrogenated at normal pressure and room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and the whole was basified with K_2CO_3. The product was extracted with dichloromethane and the extract was stirred for 15 min with NH_4OH

(dil.). The organic layer was separated, dried, filtered and evaporated. The residue was converted into the dihydrobromide salt in 2-propanone. The product was filtered off and dried, yielding 3.6 parts (70.7%) of (1-methyl-4-piperidinyl) [1-(2-phenylethyl)-1H-benzimidazol-2-yl]methanone dihydrobromide; mp. 254.8°C (comp. 38).

Example 28

A mixture of 4.5 parts of intermediate 56, 2 parts of polyoxymethylene, 2 parts of potassium acetate, 2 parts of a solution of thiophene in methanol 4%. and 119 parts of methanol was hydrogenated overnight at normal pressure and room temperature with 2 parts of palladium-on-charcoal catalyst 10%.. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was converted into the (E)-2-butenedioate (1:1) salt in ethanol. The product was filtered off and dried, yielding 2.95 parts (63.6%) of (1-methyl-4-piperidinyl) [1-(2-phenylethyl)-1H-benzimidazol-2-yl]methanone (E)-2-butenedioate (1:1); mp. 204.9°C (comp. 46).

Example 29

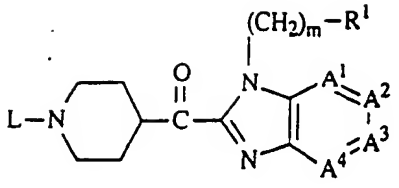
A mixture of 16 parts of compound 10 and 375 parts of hydrobromic acid 48% was stirred overnight at 80°C. The reaction mixture was evaporated and the residue was diluted with water. After basifying with NH_4OH, the product was extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated, yielding 13 parts (97.6%) of [1-(2-aminoethyl)-4-piperidinyl] [1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]methanone (comp. 11).

Example 30

To a stirred mixture of 2 parts of compound 11 and 45 parts of tetrahydrofuran there was added dropwise a solution of 1.9 parts of methyl 2-isothiocyanatobenzoate in tetrahydrofuran. After stirring for 2 hours at room temperature, the reaction mixture was evaporated. The residue was purified by column chromatography (silica gel ; $CHCl_3$ / $CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile (2x). The product was filtered off and dried, yielding 0.9 parts (32%) of 3-[2-[4-[[1-[(4-fluorophenyl)methyl]-1H-benzimidazol-2-yl]-carbonyl]-1-piperidinyl]ethyl]-2,3-dihydro-2-thioxo-4(1H)-quinazolinone; mp. 203.7°C (comp. 12).

All the other compounds listed in Table 5 were obtained by analogous methods of preparation as described in Ex. 18-30, the actual method of preparation being indicated in column 2 (Ex. No.).

Table 5



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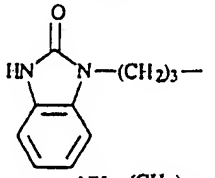
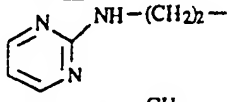
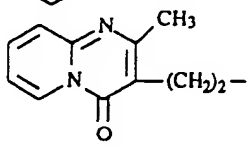
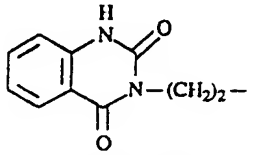
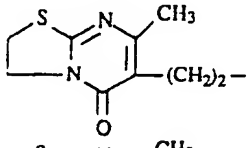
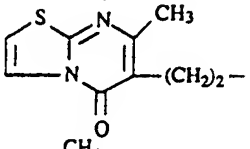
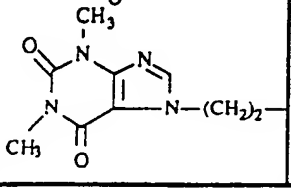
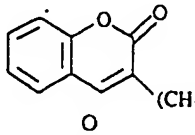
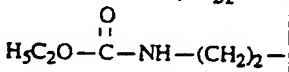
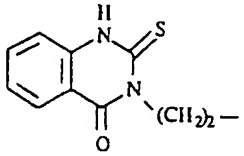
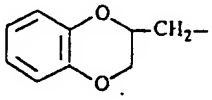
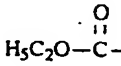
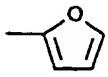
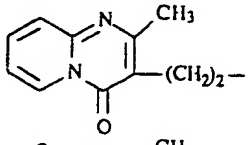
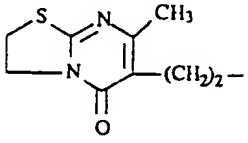
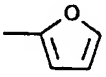
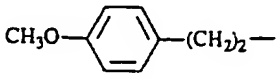
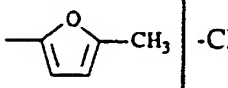
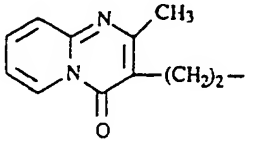
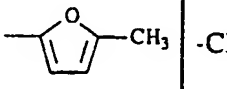
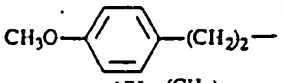
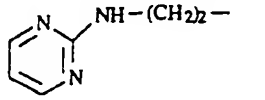
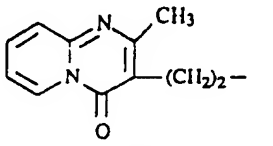
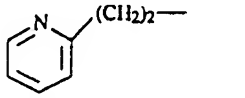
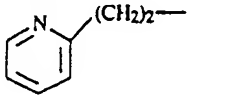
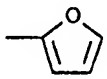
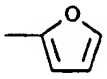
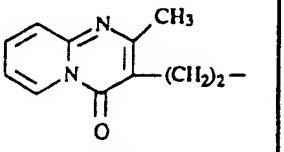
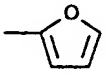
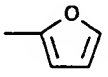
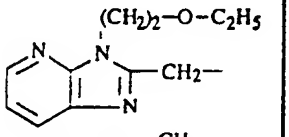
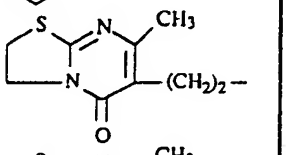
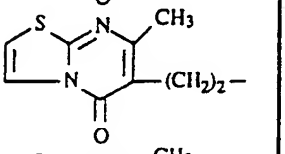
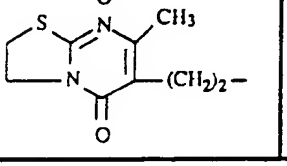
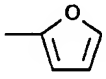
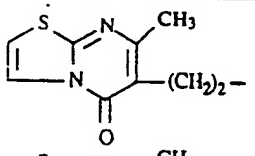
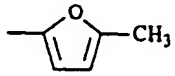
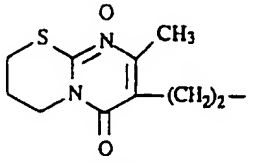
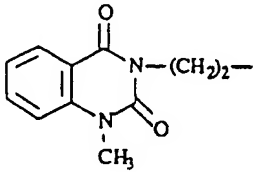
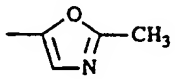
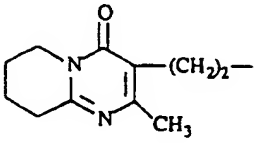
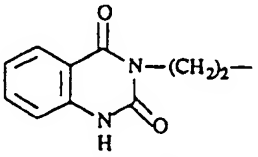
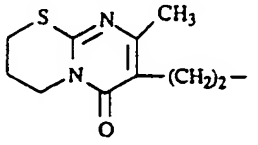
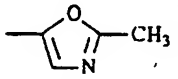
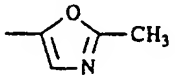
2	18		1	4-F-C_6H_4-	-CH=CH-CH=CH-	169.1°C
3	18		1	4-F-C_6H_4-	-CH=CH-CH=CH-	156.5°C
4	22		1	4-F-C_6H_4-	-CH=CH-CH=CH-	161.0°C
5	22		1	4-F-C_6H_4-	-CH=CH-CH=CH-	212.9°C
6	24		1	4-F-C_6H_4-	-CH=CH-CH=CH-	187.3°C
7	24		1	4-F-C_6H_4-	-CH=CH-CH=CH-	171.2°C
8	22		1	4-F-C_6H_4-	-CH=CH-CH=CH-	165.0°C

Co. No.	Ex. No.	L	m	R^1	$-A^1=A^2-A^3=A^4-$	physical data
9	24		1	4-F-C_6H_4-	-CH=CH-CH=CH-	147.8°C
10	22		1	4-F-C_6H_4-	-CH=CH-CH=CH-	-
11	29	NH_2-$(CH_2)_2$-	1	4-F-C_6H_4-	-CH=CH-CH=CH-	-
12	30		1	4-F-C_6H_4-	-CH=CH-CH=CH-	203.7°C
13	23		1	4-F-C_6H_4-	-CH=CH-CH=CH-	178.6°C/ $(COOH)_2$
14	19		1		-CH=CH-CH=CH-	112.3°C
15	19	H	1	4-F-C_6H_4-	-N=CH-CH=CH-	198.5°C/1*
16	26	CH_3-	1	4-F-C_6H_4-	-N=CH-CH=CH-	206.2°C/ $(COOH)_2$
17	22		1	4-F-C_6H_4-	-N=CH-CH=CH-	101.2°C
18	22		1	4-F-C_6H_4-	-N=CH-CH=CH-	126.7°C/ $(COOH)_2$
19	19	H	1		-N=CH-CH=CH-	198.1°C/ $(COOH)_2$
20	22		1	4-F-C_6H_4-	-N=CH-CH=CH-	118.2°C
21	19	CH_3-	1	4-F-C_6H_4-	-CH=CH-CH=N-	74.8°C/H_2O 2$(COOH)_2$
22	19	CH_3-	1		-CH=CH-CH=CH-	124.0°C/H_2O 2$(COOH)_2$
23	18		1		-CH=CH-CH=CH-	193.8°C/H_2O 3/2$(COOH)_2$

Co. No.	Ex. No.	L	m	R^1	$-A^1=A^2-A^3=A^4-$	physical data
24	18		1	4-F-C_6H_4-	-CH=CH-CH=N-	143.8°C
25	18		1	4-F-C_6H_4-	-CH=CH-CH=N-	112.1°C
26	18		1	4-F-C_6H_4-	-CH=CH-CH=N-	183.0°C
27	18		1	4-F-C_6H_4-	-CH=CH-CH=N-	118.3°C 3$(COOH)_2$
28	18		1		-CH=CH-CH=CH-	181.5°C/ 2$(COOH)_2$
29	18	CH_3-	1		-N=CH-CH=CH-	180.3°C/ $(COOH)_2$
30	18		1		-N=CH-CH=CH-	167.9°C
31	18	CH_3-	1		-CH=CH-CH=CH-	195.6°C/ $(COOH)_2$
32	25		1	4-F-C_6H_4-	-CH=CH-CH=CH-	141.0°C
33	18		1	4-F-C_6H_4-	-CH=CH-CH=N-	208.9°C
34	18		1	4-F-C_6H_4-	-CH=CH-CH=N-	214.8°C
35	18		1		-N=CH-CH=CH-	205.3°C/1*

Co. No.	Ex. No.	L	m	R^1	$-A^1=A^2-A^3=A^4-$	physical data
36	18		1		-CH=CH-CH=CH-	149.7°C
37	18		1	$4\text{-F-}C_6H_4$-	-CH=CH-CH=CH-	159.6°C
38	27	CH_3-	2	C_6H_5-	-CH=CH-CH=CH-	254.8°C/ 2HBr
39	18		1	$4\text{-F-}C_6H_4$-	-CH=CH-CH=CH-	-
40	27	CH_3-	1		-CH=CH-CH=CH-	83.5°C/2H_2O
41	18		1	$4\text{-F-}C_6H_4$-	-CH=CH-CH=CH-	-
42	18		1	$4\text{-F-}C_6H_4$-	-CH=CH-CH=CH-	-
43	18		1	$4\text{-F-}C_6H_4$-	-CH=CH-CH=N-	-
44	20	$(CH_3)_3C\text{-O-CO-}$	1		-CH=CH-CH=CH-	-
45	21	H	1		-CH=CH-CH=CH-	176.2°C/3/2 *
46	28	CH_3-	2	C_6H_5-	-CH=CH-CH=CH-	204.9°C/*
47	28	CH_3-	1	C_6H_5-	-CH=CH-CH=CH-	168.9°C/*
48	28	CH_3-	2	$4\text{-F-}C_6H_5$-	-CH=CH-CH=CH-	3/2 HCl

* = (E)-2-butenedioate

C. Pharmacological example

Example 31

The useful antihistaminic properties of the compounds of formula (I) can be demonstrated in the test "Protection of rats from compound 48/80-induced lethality", which is described in US-4,556,660, incorporated herein by reference. The ED_{50}-value (in mg/kg) for the compounds 6; 17; 25; 26; 27; 28; 30 or 40 was found to range from 0.02 mg/kg to 0.04 mg/kg.

D. Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 32 : Oral drops

500 g of the A.I. is dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there are added 35 l of polyethylene glycol and the mixture is stirred well. Then there is added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there are added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of the A.I. The resulting solution is filled into suitable containers.

Example 33 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example 34 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The

resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example 35 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinyl-pyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example 36 : Injectable solutions

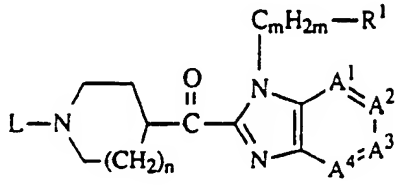
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate are dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there are added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I..The solution is cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution is sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 37 : Suppositories

3 g A.I. is dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN®) and triglycerides (Witepsol 555®) q.s. ad 300 g are molten together. The latter mixture is mixed well with the former solution. The thus obtained mixture is poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg of the A.I.

Claims

1. A compound having the formula :



(I),

a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

$-A^1=A^2-A^3=A^4-$ is a bivalent radical having the formula

-CH=CH-CH=CH-	(a-1),
-N=CH-CH=CH-	(a-2),
-CH=N-CH=CH-	(a-3),
-CH=CH-N=CH-	(a-4),
-CH=CH-CH=N-	(a-5),
-N=CH-N=CH-	(a-6) or
-CH=N-CH=N-	(a-7);

wherein one or two hydrogen atoms in said radicals (a-1) to (a-7) may each independently be replaced by halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy or trifluoromethyl;

R^1 is aryl[1] or a radical of formula -D-R^2 wherein D is O or S; R^2 is C_{1-6}alkyl optionally substituted with hydroxy, C_{1-6}alkyloxy, carboxyl or C_{1-6}alkyloxycarbonyl;

m is 1, 2, 3 or 4;

n is 0, 1 or 2 ;

L is hydrogen; C_{1-12}alkyl; C_{3-6}cycloalkyl; C_{3-6}alkenyl optionally substituted with aryl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; or a radical of formula :

-Alk-R^3	(b-1);
-Alk-Y-R^4	(b-2);
-Alk-Z^1-C(=X)-Z^2-R^5	(b-3);
-CH_2-CHOH-CH_2-O-R^6	(b-4); or
-Alk-CHOH-R^{14}	(b-5); wherein

Alk is C_{1-6}alkanediyl;

R^3 is cyano, aryl or Het;

R^4 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^5 is hydrogen, aryl, Het or C_{1-6}alkyl optionally substituted with aryl or Het;

R^6 is aryl or naphthalenyl;

R^{14} is aryl;

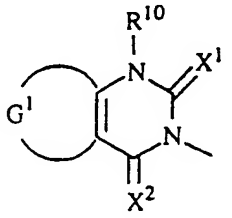
Y is O, S, NR^7; said R^7 being hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl ;

Z^1 and Z^2 each independently are O, S, NR^8 or a direct bond; said R^8 being hydrogen or C_{1-6}alkyl;

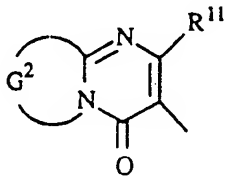
X is O, S or NR^9; said R^9 being hydrogen, C_{1-6}alkyl or cyano;

each Het is selected from pyridinyl optionally substituted with one or two substituents each independently selected from halo, amino, mono- and di(C_{1-6}alkyl)-amino, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy and hydroxy; pyrimidinyl optionally substituted with one or two substituents each independently selected from halo, amino, C_{1-6}alkylamino, C_{1-6}alkyl and C_{1-6}alkyloxy; pyridazinyl optionally substituted with C_{1-6}alkyl or halo; pyrazinyl optionally substituted with halo, amino or C_{1-6}alkyl; thienyl optionally substituted with halo or C_{1-6}alkyl; furanyl optionally substituted with halo or C_{1-6}alkyl; pyrrolyl optionally substituted with C_{1-6}alkyl; thiazolyl optionally substituted with C_{1-6}alkyl; imidazolyl optionally substituted with one or two substituents each independently selected from C_{1-6}alkyl, arylC_{1-6}alkyl and nitro; 1,3,4-thiadiazolyl optionally substituted with C_{1-6}alkyl or amino; oxazolyl optionally substituted with C_{1-6}alkyl; 2,3-dihydro-1,4-benzodioxinyl optionally substituted with C_{1-6}alkyl or halo; 2-oxo-2H-1-benzopyranyl and 4-oxo-4H-1-benzopyranyl both being optionally substituted with C_{1-6}alkyl; 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl optionally substituted with C_{1-6}alkyl; 6-purinyl; and

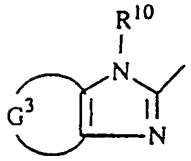
a bicyclic heterocyclic radical of formula



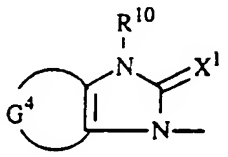
(c-1),



(c-2),



(c-3),



(c-4),

wherein

X^1 and X^2 each independently are O or S ;

each R^{10} is hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl;

R^{11} is hydrogen, C_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, halo or C_{1-6}alkyloxycarbonylC_{1-6}alkyl ;

G^1 is -CH=CH-CH=CH-; -S-CH=CH- or -N=CH-NH- ;

G^2 is -CH=CH-CH=CH-, $-(CH_2)_4$-, $-S-(CH_2)_2$-, $-S-(CH_2)_3$-, -S-CH=CH-, -CH=CH-O-, $-NH-(CH_2)_2$-, $-NH-(CH_2)_3$-, -NH-CH=CH-, -NH-CH=N-, -NH-N=CH- or $-NH-N=CH-CH_2$-;

G^3 is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

G^4 is -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH- or -CH=N-CH=N- ;

wherein one or two hydrogen atoms in said radicals G^1, G^2, G^3 or G^4 may be replaced by C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxy or halo, when connected to a carbon atom; or by C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl or arylC_{1-6}alkyl when connected to a nitrogen atom;

each aryl is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl;

each $aryl^1$ is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, nitro, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, mercapto, amino, mono- and di(C_{1-6}alkyl)amino, carboxyl, C_{1-6}alkyloxycarbonyl and C_{1-6}alkylcarbonyl; thienyl; halothienyl; furanyl optionally substituted with C_{1-6}alkyl and/or hydroxyC_{1-6}alkyl; pyridinyl optionally substituted with C_{1-6}alkyl; pyrimidinyl; pyrazinyl; thiazolyl optionally substituted with C_{1-6}alkyl; imidazolyl optionally substituted with C_{1-6}alkyl; or oxazolyl optionally substituted with one or two C_{1-6}alkyl or hydroxyC_{1-6}alkyl radicals;

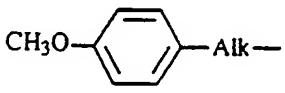
provided that when $-A^1=A^2-A^3=A^4-$ is a radical of formula (a-1) and R^1 is phenyl optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxy, halo or hydroxy; then L is other than hydrogen, C_{1-6}alkyloxycarbonyl or other than a radical of formula -Alk-R^3 (b-1),

-Alk-O-R^4 (b-2-a), -Alk-C(=O)-R^5 (b-3-a) or -Alk-CHOH-R^{14} (b-5)wherein R^3, R^4, R^5 and R^{14} are phenyl optionally substituted with halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy.

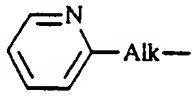
2. A compound according to claim 1 wherein -A^1=A^2-A^3=A^4- is a bivalent radical of formula (a-1), (a-2) or (a-5); R^1 is phenyl optionally substituted with halo, furanyl optionally substituted with C_{1-6}alkyl, or oxazolyl optionally substituted with C_{1-6}alkyl; m is 1 or 2; n is 1; L is hydrogen, C_{1-12}alkyl, C_{1-6}alkyloxycarbonyl, or a radical of formula (b-1), (b-2) or (b-3), wherein R^3 is cyano, aryl or Het; R^4 is hydrogen or Het; R^5 is C_{1-6}alkyl; Y is O or NH; Z^1 and Z^2 each independently are NH or a direct bond; X is O; each Het is selected from pyridinyl, pyrimidinyl, thiazolyl, 2,3-dihydro-1,4-benzo-dioxinyl, 2-oxo-2H-1-benzopyranyl, 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purin-7-yl, or a bicyclic heterocyclic radical of formula (c-1), (c-2), (c-3) or (c-4), wherein X^1 and X^2 each independently are O or S ; each R^{10} is hydrogen, C_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; each R^{11} is C_{1-6}alkyl; G^1 is -CH=CH-CH=CH-; G^2 is -CH=CH-CH=CH-, -$(CH_2)_4$-, -S-$(CH_2)_2$-, -S-$(CH_2)_3$-, -S-CH=CH-; G^3 is -N=CH-CH=CH-; G^4 is -CH=CH-CH=CH-; aryl is phenyl optionally substituted with C_{1-6}alkyloxy.

3. A compound according to claim 2 wherein m is 1, L is C_{1-4}alkyl or a radical of formula (b-1) or (b-2), wherein R^3 is aryl or Het; R^4 is Het; Y is NH; each Het is selected from pyridinyl, pyrimidinyl, or a bicyclic heterocyclic radical of formula (c-2), wherein R^{11} is C_{1-6}alkyl; G^2 is -CH=CH-CH=CH-, -S-$(CH_2)_2$-, -S-$(CH_2)_3$-, -S-CH=CH-; aryl is phenyl optionally substituted with C_{1-6}alkyloxy.

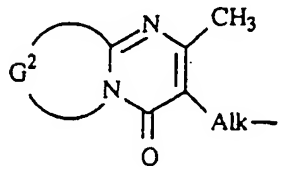
4. A compound according to claim 3 wherein R^1 is halophenyl, furanyl optionally substituted with methyl, or oxazolyl optionally substituted with methyl; L is methyl or a radical of formula :



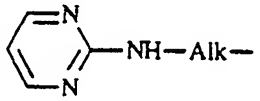
(d-1) ;



(d-2) ;



(d-3) ; or



(d-4).

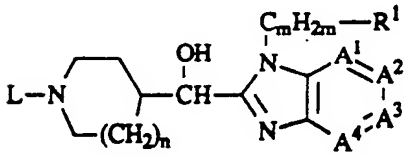
5. An antiallergic composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective antiallergic amount of a compound as claimed in any of claims 1 to 4.

6. A process for preparing an anti-allergic composition as claimed in claim 5, characterized in that a therapeutically effective antiallergic amount of a compound of formula (I) as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.

7. A compound as claimed in any of claims 1 to 4 for use as a medicine.

8. A process of preparing a compound as claimed in any of claims 1 to 4, characterized by :

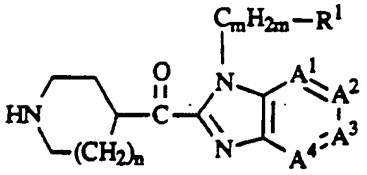
a) oxidizing an alcohol derivative of formula



(II)

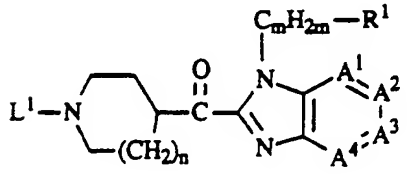
with an oxidizing agent in a reaction-inert solvent;

b) N-alkylating a compound of formula



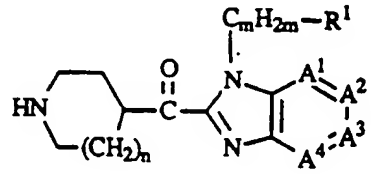
(I-b)

with an alkylating reagent of formula L^1-W (III) wherein L^1 represents L but is other than hydrogen and W represents a reactive leaving group, in a reaction-inert solvent in the presence of a base and optionally in the presence of a iodide salt, thus yielding a compound of formula



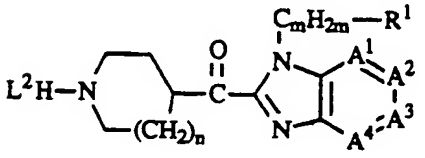
(I-a)

c) reductively N-alkylating a compound of formula



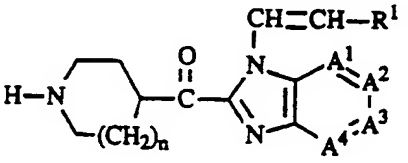
(I-b)

with a ketone or an aldehyde of formula L^2=O (IV) wherein L^2=O represents an intermediate of L^2H^2 wherein two geminal hydrogen atoms are replaced by =O, and L^2 represents C_{1-12}alkylidene, C_{3-6}cycloalkylidene, R^3-C_{1-6}alkylidene, R^4-Y-C_{1-6}alkylidene, or R^5-Z^2-C(=X)-Z^1-C_{1-6}alkylidene by reducing a mixture of the reactants in a reaction-inert solvent with a reducing agent or alternatively in the presence of hydrogen and a hydrogenation catalyst; thus yielding a compound of formula (I-a-1)



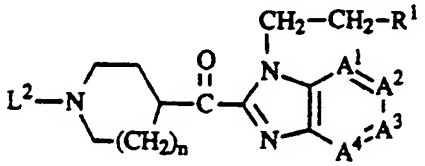
(I-a-1)

d) reductively N-alkylating an intermediate of formula



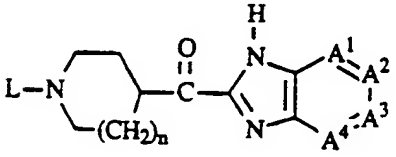
(V)

with a reagent of formula L^2=O (IV) in the presence of hydrogen and a hydrogenation catalyst in a reaction-inert solvent; thus yielding a compound of formula (I-a-2)



(I-a-2)

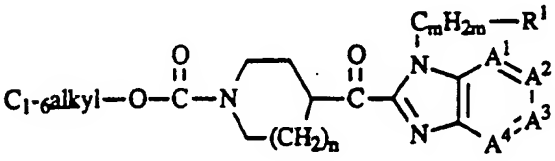
e) N-alkylating an intermediate of formula



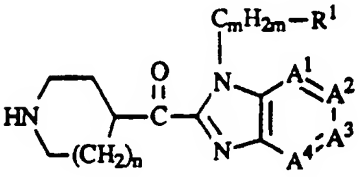
(VI)

with an alkylating reagent of formula R^1-C_mH_{2m}-W in a reaction-inert solvent in the presence of a base and optionally in the presence of a iodide salt;

f) converting a compound of formula

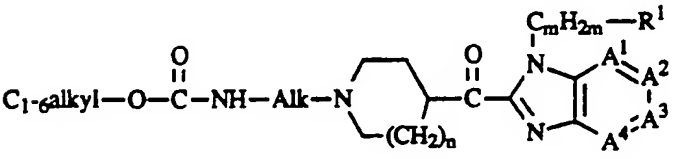


by treatment with an acid, into a compound of formula

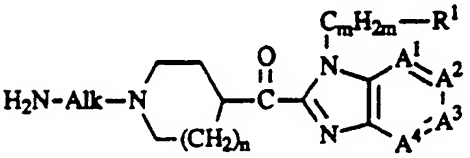


(I-b) ;

g) converting a compound of formula

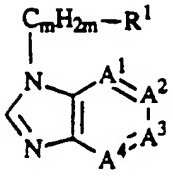


by treatment with an aqueous acidic solution into a compound of formula



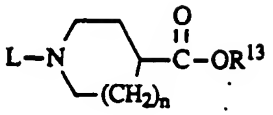
;

h) reacting an intermediate of formula



(XVII)

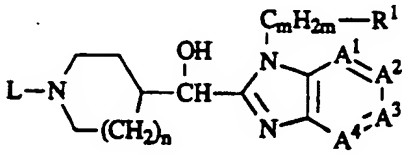
with a strong base in a reaction-inert solvent and subsequently acylating the thus obtained salt form of (XVII) with a piperidinyl derivative of formula



(XVI);

and, if desired, optionally further converting the compounds of formula (I) into each other following functional group transformation reactions; and, if desired, converting the compounds of formula (I) into a therapeutically active non-toxic acid addition salt form by treatment with an acid; or conversely, converting the acid salt into the free base with alkali; and/or preparing stereochemically isomeric forms thereof.

9. A compound having the formula :



(II)

a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein $-A^1=A^2-A^3=A^4-$, R^1, m, n and L are as defined in claim 1.

10. A method of treating warm-blooded animals suffering from allergic diseases comprising administering to said warm-blooded animals an effective anti-allergic amount of a compound as claimed in any of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01782

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 401/06 A 61 K 31/445 C 07 D 401/14
C 07 D 405/14 C 07 D 413/14 C 07 D 471/04 C 07 D 473/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 401/00 C 07 D 405/00 C 07 D 413/00 C 07 D 471/00 C 07 D 473/00 C 07 D 513/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0363963 (MERRELL DOW PHARMACEUTICALS) 18 April 1990, see page 17, claim 1; pages 14-16, examples III,V,VI,VIII; page 12, lines 43-44 (cited in the application) ---	1-4,7
Y	EP,A,0151826 (JANSSEN PHARMACEUTICA N.V.) 21 August 1985, see pages 120-123, claim 1; pages 38-108g, examples; page 116, lines 1-5 (cited in the application) ---	1-4,7
A	EP,A,0206415 (JANSSEN PHARMACEUTICA N.V.) 30 December 1986, see pages 80-83, claim 1; pages 45-73, examples; page 36, lines 13-17 (cited in the application) --- -/-	1-4,7

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05-12-1991	13. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	EP,A,0070053 (JANSSEN PHARMACEUTICA N.V.) 19 January 1983, see pages 50-51, claim 1; pages 43-44, examples XIII,XIV; page 18, lines 5-8	1-4,7

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9101782 SA 51080

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/02/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0363963	18-04-90	US-A-	4908372	13-03-90
		AU-A-	4273589	26-04-90
		CA-A-	2000468	13-04-90
		JP-A-	2134377	23-05-90
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		AU-A-	3736485	12-09-85
		CA-A-	1259609	19-09-89
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		SU-A-	1396964	15-05-88
		US-A-	4839374	13-06-89
		US-A-	4695575	22-09-87
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		AU-B-	547967	14-11-85
		AU-A-	8575982	20-01-83
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		JP-A-	58018390	02-02-83
		SU-A-	1138032	30-01-85
		US-A-	4548938	22-10-85
		US-A-	4529727	16-07-85